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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. PRIMARY MALIGNANT LIVER NEOPLASMS IN CHILDREN.

Shabanov MA

Dept. Pathology of Human Tumors, All-Union Cancer Res. Center, Moscow, USSR

Arkh Patol; 43(7):84-90 1981

Literature data on the incidence, etiology, and pathogenesis of primary malignant liver neoplasms in children are reviewed. Frequent association between liver neoplasms and congenital defects is indicative of a similar pathogenetic mechanism of hepatoblastomas, Wilms' tumors, and adrenocortical tumors. Hepatoblastomas are predominant in children less than 3 yr, while hepatocarcinomas are predominant i n children greater than 3 yr. Male:female ratio for hepatoblastomas is 2.5:1, compared with 11:1 for hepatocarcinomas. Histological classifications recognize anaplastic, embryonal, fetal, and adult cellular variants of primary liver tumors. Mixed hepatoblastomas contain epithelial and spindle like mesenchymal cells. Characteristic feature of hepatocellular carcinomas is the presence of giant multinuclear cells. (75 Refs) (In RUS)

2. HEPATOMA IN SIBLINGS WITH PROGRESSIVE FAMILIAL CHOLESTATIC CIRRHOSIS OF CHILDHOOD.

Ugarte N, Gonzalez-Crussi F

(c/o Gonzalez-Crussi) Dept. Pathology, Children's Memorial Hosp., 2300 North Children's Plaza, Chicago, IL, 60614

Am J Clin Pathol; 76(2):172-177 1981

This report describes four siblings affected with familial intrahepatic cholestasis detected in early infancy. In the two male siblings, biliary cirrhosis and fatal hepatocellular carcinoma later developed, whereas the female siblings have had persistent hepatomegaly and recurrent episodes of cholestasis. Sequential biopsies show that this rare disorder of unknown etiology must be added to the many causes of giant cell transformation of the liver in infancy. Its oncogenic risk, particularly in males, has not been generally appreciated. (Author abstract) (29 Refs)

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N

Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

J Surg Oncol; 18(1):73-85 1981

Studies involving the role of oral contraceptive use in the etiology of benign and malignant liver tumors are reviewed. The evidence from these studies strongly suggests that there is a relationship between the use of oral contraceptives and benign liver tumors. The actual risk appears related to duration of usage and may also be related to the type of contraceptive steroid used. Further investigation is required to determine the oncogenic potential of oral contraceptives and the malignant potential of benign tumors. (Author abstract) (62 Refs)

4. POSSIBLE ASSOCIATION OF ANGIOSARCOMA WITH ORAL CONTRACEPTIVE AGENTS.

Shi EC, Fischer A, Crouch R, Ham JM
(c/o Ham) Dept. Surgery, Prince Wales Hosp., Randwick, New South Wales 2031, Australia
Med J Aust; 1(9):473-474 1981

Angiosarcoma of the liver has been reported to be associated with the long-term use of androgenic-anabolic and estrogenic steroids. It has been suggested that this tumor might develop in women after long-term exposure to oral contraceptive steroids, although this association has not yet been reported. We present here the clinical and pathological findings in a 42-yr-old woman who died of hepatic angiosarcoma after taking oral contraceptive steroids for 10 yr. (Author abstract) (13 Refs)

5. SOURCE OF DRINKING WATER AT HOME AND SITE-SPECIFIC CANCER INCIDENCE IN WASHINGTON COUNTY, MARYLAND.

Wilkins JR, Comstock GW
Dept. Preventive Medicine, Ohio State Univ., 410 West Tenth Ave., Columbus, OH, 43210
Am J Epidemiol; 114(2):178-190 1981

A nonconcurrent prospective study was conducted to investigate the postulated relationship between organic chemical by-products of water chlorination and risk of human cancer. Vital records and nonofficial census data available for each of nearly 31,000 study subjects were used to compute selected sex- and site-specific cancer incidence rates in a well-defined county population. Age, socioeconomic status, smoking history, source of drinking water at home, and other individual characteristics of the study population were examined in relation to the cancer rates. The drinking water source variable consisted of three historical cohorts, each distinguished by a different degree of exposure to chloroform and other chlorination by-products. Incidence rates for cancer of the bladder among men and for cancer of the liver among women were nearly twofold higher in the drinking water cohort that had been supplied chlorinated surface water at home when compared to the cohort with a history of consumption of unchlorinated ground water. The differences, however, were not statistically significant. A complementary mortality study also suggested an association of chlorinated water with cancer of the liver and urinary tract. The findings in Washington County indicate the need for further studies of individuals with different histories of exposure to chlorinated and unchlorinated drinking water. (Author abstract) (49 Refs)

6. INCREASING FREQUENCY OF PRIMARY LIVER CARCINOMA IN THE CANTON OF ZURICH.

Maurer R, Schuler G, Bosch R, Ruttner J
Institut fur Pathologie, Universitatspital, 8091 Zurich, Switzerland
Praxis; 70(27):1222-1227 1981

The occurrence of liver cirrhosis (LC) and primary liver carcinoma (PLC) was studied in 39,336 consecutive autopsies performed in the Canton of Zurich during the period 1967-1978. The autopsies represented 34% of all deaths during the observation period. PLC was found in 405 cases (313 men and 92 women), LC in 2,368 cases (1,605 men and 763 women). PLC was associated with LC in 299 cases (252 men and 47 women). The proportion of PLC increased during the observation period from 0.68% in 1967 to 1.51% in 1978, while the proportion of LC remained fairly constant at approx 6%. There was an increase in the proportion of PLC both with and without LC. The age and sex distribution of PLC shows a predilection for men aged 50-79 yr. There was a 50% increase in the occurrence of PLC among men in their 60s and 70s, while cirrhosis remained constant in men of this age group. It is concluded that there has been a real increase in the incidence of PLC, which can not be explained by the higher proportion of old people in the population, nor by an increased frequency of LC. This assumption is also supported by increased mortality due to PLC in the Swiss federal mortality statistics. Aflatoxins are unlikely to have been a significant etiological factor. (22 Refs) (In GER)

7. MORTALITY FROM CANCER OF THE DIGESTIVE SYSTEM IN ITALY: 1950-1975 CROSS-SECTIONAL RATES AND COHORT ANALYSIS.

Mastrandrea V, La Rosa F, Cresci A, Pannelli F
(c/o La Rosa) Inst. Hygiene, Camerino Univ., 62032 Camerino, Italy
Am J Epidemiol; 114(2):218-228 1981

In this study of mortality from cancer of the digestive system in Italy, 1950-1975, both cross-sectional rates and cohort analysis were used. The study found that in both sexes age-standardized rates for cancer of the colon, rectum, liver and biliary tract, and pancreas are increasing whereas the rates for cancer of the stomach are decreasing. Rates for esophagus cancer have remained fairly constant. Cohort analysis showed different trends for selected sites. As to cancer of the stomach, for both sexes, cohorts born up until about 1881 have constant or increasing rates; cohorts born after 1881 have declining rates. For cancer of the esophagus in males the rates reach a peak in the 1896 birth-cohort; cohorts born prior to 1896 show an increase in rates and cohorts born later show a decline. For cancer of the colon, liver and biliary tract, and pancreas, the rates rise constantly for all ages and all cohorts in both sexes. The rates for cancer of the rectum rise after age 75 whereas below that age the rates tend to level off and decline. (Author abstract) (40 Refs)

8. THE HEPATOMAS.

Bogliaccini G, Pomi J, Bagnulo H, Praderi R
Clinica Quirurgica '3'. Hospital Maciel, Facultad de Medicina, Juan Paullier 1110, Apto 16, Montevideo, Uruguay
Cir Urug; 51(2):127-130 1981

The hepatomas are of low frequency in Uruguay. The 33 cases were of the 438,700 patients registered in Hospitals between 1951-1970 and only 25 had hepatomas or 0.005%. The 33 cases presented were from 9-80 yr, most were 50-70 yr and av age was 56.7 yr. The majority 28 patients were men and only 5 women. There was a high incidence 45% of cirrhosis, all cases were men. The 29 were hepatocarcinomas and 4 cholangiocarcinomas. Of the 16 patients that had exploratory surgery, 5 were resected and one of this last group was still living 25 mo later, working and in excellent state of health. (20 Refs) (In SPA)

9. MORBIDITY FROM CANCER IN LA PAZ, BOLIVIA.

Rios-Dalenz J, Correa P, Haenszel W
Casilla 490. La Paz, Bolivia
Int J Cancer; 28(3):307-314 1981

Data from a population-based Cancer Registry in La Paz, Bolivia, are presented. The city is located at approx 4,000 meters above sea level and has a strong cultural influence consisting of Aymara Indians immigrating from the altiplano. Incidence rates in females are high for cancer of the cervix, the gallbladder and the thyroid gland. Males display unusually high rates of testicular cancer. Stomach cancer rates are lower than among other Andean populations. Smoking-related cancer and cancers related to sex-hormones are lower than av in incidence. Cancer of the nasal mucosa and paranasal sinuses is unusually high in frequency. (Author abstract) (20 Refs)

TUMOR INDUCTION IN ANIMALS

10. EXISTENCE OF A PRACTICAL THRESHOLD DOSE FOR THE HEPATOCARCINOGEN 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE IN RAT LIVER.

Hino O, Kitagawa T
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Gan; 72(4):637-638 1981

The possible existence of a threshold dose for the potent hepatocarcinogen 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB) was examined in male Donryu rats. The rats were divided into eight groups (Groups 1-8) and were fed a diet containing 0, 1, 5, 10, 20, 60, 100, and 300 ppm 3'-Me-DAB, respectively. There was a small number of enzyme-altered islands (EAI)/square cm/rat in the livers of control rats (Group 1) at 36 wk of age. Apparently high incidences of EAI were scored from the livers of animals from Groups 6-8 (60, 100, and 300 ppm). However, the incidence in Group 5 rats (20 ppm) suddenly dropped to a level less than one-seventh that of the control group. The incidences of EAI in Groups 2-4 were also below that of the control animals. An inverted dose-effect relation was clearly demonstrated. The difference in EAI incidence between control Group 1 and Group 5 (20 ppm) was statistically significant (p less than 0.01). These results suggested that there is a practical threshold for 3'-Me-DAB between 20 and 60 ppm. (6 Refs)

11. HEPATOCELLULAR CARCINOMA INDUCED BY ESTROGEN AND PROGESTOGEN: DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RATS FOLLOWING ORAL ADMINISTRATION OF SYNTHETIC ESTROGEN AND PROGESTOGEN.

Higashi S
First Dept. Surgery, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):295-303 1981

Female Wistar rats were given daily 0.075 mg of ethinyl-estradiol (EES) and 6 mg of norethindrone acetate (NEA) dissolved in olive oil by gavage for 1 yr, another group received similar treatment for 18 mo, and a third group received olive oil alone for 1 yr and served as controls for the first group. In rats treated with EES and NEA, the liver wt increased markedly, while the body wt decreased. In the rats treated for 18 mo, the activities of glutamine oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase were higher and total cholesterol and triglyceride were lower, than those treated for only 1 yr. Multiple nodules ranging from 0.2 mm to 1 mm in diameter were observed in all the treated rats. These were hyperplastic nodules with compression and atrophy of the surrounding liver parenchyma. One of the 18 rats in the first group had a large, 2.5 x 2.0 x 1.5 cm, well-differentiated hepatocellular carcinoma composed of trabeculae of neoplastic cells. In rats treated for 18 mo, the number of hyperplastic nodules was higher and their size was larger than animals treated for 12 mo. These results support the hypothesis that EES and NEA may be initiators in hepatocarcinogenesis. (30 Refs)

12. CARCINOGENESIS IN SYRIAN HAMSTERS BY N-NITROSO-2,6-DIMETHYLMORPHOLINE, ITS CIS AND TRANS ISOMERS, AN THE EFFECT OF DEUTERIUM LABELING.

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Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611

Carcinogenesis; 2(8):731-735 1981

Syrian golden hamsters were divided into groups of 20 each. They were given doses of N-nitroso-2,6-dimethylmorpholine (NDMM), its cis or trans isomer, or its alpha-d4 or beta-d2 deuterium-labeled derivatives. The weekly doses (mg/kg body wt) were NDMM 18 or 50; cis-NDMM 11.5 or 31; trans-NDMM 6.5 or 17; d4 18 or 50; d2 50. A total of 52 benign and 21 malignant tumors resulted, most associated with the pancreas, liver, respiratory system, and kidneys. The survival rate among hamsters treated with cis-NDMM was about the same as the rate for those treated with NDMM. The survival rate with trans-NDMM was higher, indicating that trans-NDMM was a less potent carcinogen. Treatment with d4 produced tumors earlier than treatment with d2, suggesting that d4 was the more potent of the two. The overall incidences of malignant tumors for the NDMM, d4, and d2 groups were not significantly different. Activation to mutagenicity by pancreas microsomes, and binding to DNA of the pancreas did not differ between the isomers. (21 Refs)

13. THE ROLE OF TOXICITY IN THE CARCINOGENICITY OF ENDOSULFAN.

Reuber MD

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Sci Total Environ; 20(1):23-47 1981

Two NCI studies examined toxicity and carcinogenicity of endosulfan (ES; 6,7,8,9,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9, methano-2,4,3-benzodioxathiepin-3-oxide; Thiodan) in groups of Osborne Mendel rats and B6C3F1 mice. Male rats initially received 281 or 562 ppm of ES in the diet; females received 89 or 178 ppm. The doses were adjusted upwards to av 408 or 952 ppm (males) and 223 or 445 (females) during the 105-106 wk period of observation. Over a 92 wk span, male mice ingested 3.5 or 6.9 ppm of ES and females ingested 2 or 3.9 ppm. In rats ES significantly increased mortality. Both male and female rats developed lymphosarcoma and benign and malignant neoplasms at all sites; male rats showed high incidence of endocrine neoplasms while females exhibited high incidence of neoplasms of the reproductive system. Chronic interstitial fibrosis was the cause of death in most male rats on either dose. Lesions of the parathyroid gland were related to renal disease. Osteitis fibrosis was found in many male but few female rats. In the mice, ES favored survival compared to controls. In female mice, carcinomas of the liver were found in 6/17 mice on the low dose of ES compared to 1/17 controls. While male mice did not show increased incidence of neoplasms, they developed amyloidosis and chronic inflammation of the kidney. A review includes every known study on carcinogenicity of ES in animals. (35 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

14. EFFECTS OF 2-AND 3-TERT-BUTYL-4-HYDROXYANISOLE ON GLUTATHIONE S-TRANSFERASE AND EPOXIDE HYDROLASE ACTIVITIES AND SULFHYDRYL LEVELS IN LIVER AND FORESTOMACH OF MICE.

Lam LK, Sparnins VL, Hochalter JB, Wattenberg LW
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Cancer Res; 41(10):3940-3943 1981

Butylated hydroxyanisole, a food additive, has been found to inhibit the neoplastic effects of a wide variety of chemical carcinogens. The commercially available preparations of butylated hydroxyanisole contain two isomers, 2-tert-butyl-4-hydroxyanisole (2-BHA) and 3-tert-butyl-4-hydroxyanisole (3-BHA). Both isomers induce increased activities of glutathione (GSH) S-transferase and epoxide hydrolase and increase acid-soluble sulfhydryl concentration in hepatic and forestomach tissues of A/HeJ mice. The inductions were assayed after 2 wk of feeding diets containing the two isomers. 3-BHA induced an increase in the activity of hepatic microsomal epoxide hydrolase by 1.4x that of the control. The activity of cytosol GSH S-transferase was enhanced by both isomers. In the liver, the 3-BHA induction was more than 3x higher than that of 2-BHA. In the forestomach, however, the induction effect of the two isomers was reversed. The overall magnitude of the induction was much lower in the forestomach than in the liver. Synergistic effects on the induction of GSH S-transferase activity were observed in the forestomach cytosol when mixtures of different proportions of the two isomers were added to the diet. Max enzyme activity was obtained at a ratio of 75% 2-BHA and 25% 3-BHA. No synergistic effect was observed with the corresponding hepatic cytosolic enzyme. The relative inductive effects of 2-and 3-BHA on the acid-soluble sulfhydryl level of liver and forestomach tissues followed closely those on GSH S-transferase activity. The results of the present study show that the two isomers of butylated hydroxyanisole differ in the magnitude of their effects on carcinogen-metabolizing systems of the liver and forestomach. (Author abstract) (27 Refs)

15. INFLUENCE OF ETHYL ALCOHOL ON CARCINOGENESIS WITH N-NITROSODIMETHYLAMINE.

Griciute L, Castegnaro M, Bereziat JC
Inst. Epidemiology, Microbiology, and Hygiene, 64 Gorki St., Vilnius 232024, Lithuania, USSR
Cancer Lett; 13(4):345-352 1981

The carcinogenic action of N-nitrosodimethylamine (NDMA; 0.03 mg by gavage x 2/wk) administered for 50 wk in either water or 40% ethanol was examined in 208 C57BL 8-wk-old mice. The mice were divided into the following treatment groups: (1) NDMA in ethanol, (2) NDMA in water, and (3) ethanol only. Death from tumors in groups 1 and 2 began, respectively, at wk 30 and 38; all group 3 subjects survived beyond 50 wk. Most notably, frontal brain lobe malignant tumors appeared only in group 1. Greyish infiltrating masses arising from the posterior nasal fossa were detected in 12/36 males and 12/30 females. Tumors were microscopically identical; histological appearance was typical of olfactory neuroepithelioma. No metastases were found. Groups 1 and 2 exhibited other malignant and benign liver tumors and lymphomas. Lymphomas and benign tumors were also found in group 3.

Tumor rate (21%) was significantly lower in group 3 than in groups 1 (48%) and 2 (43%); morbidity for malignant liver tumors was significantly lower in group 1 (16%) than in group 2 (30%). Alcohol by itself was not carcinogenic but was associate a change in target for the liver carcinogen NDMA: development of infiltrating olfactory neuroepithelioma was favored. (14 Refs)

16. PROMOTIVE EFFECTS OF DEOXYCHOLIC ACID ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE IN MALE RATS.

Cameron R, Imaida K, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 72(4):635-636 1981

The ability of deoxycholic acid (DA), administered over a short time period, to promote the appearance of hyperplastic foci or hyperplastic nodules in diethylnitrosamine (DEN)-initiated male Fischer rats was examined. The 80 rats were divided into five groups, 15 rats in Groups 1-4 and 20 rats in Group 5. Groups 1, 3, and 5 were injected ip with DEN and later Groups 1 and 3 were fed 0.5% DA or 0.05% phenobarbital (PB), respectively, for 10 wk. Groups 2 and 4 were given saline in place of DEN and later fed DA or PB alone for 10 wk. Both DA and PB (Groups 1 and 3) promoted the development of considerable numbers of foci positive for gamma-glutamyl transferase if preceded by DEN initiation. DEN alone (Group 5) induced much fewer and relatively small foci but induced no hyperplastic nodules. Significantly more and larger foci and a considerably greater number of hyperplastic nodules were seen with DA (Group 1) than with PB (Group 3). DA without DEN (Group 2) induced a small number of foci and hyperplastic nodules. These data suggested that DA is a moderately strong promoter of preneoplastic liver lesions in the male rat. (9 Refs)

17. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

Kiessling M, Lipinski R, Bohm N, Kleihues P
Pathologische Institut, Universitat Freiburg, 78 Freiburg, W. Germany
Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

18. PROTECTIVE ROLE OF THE GLUTATHIONE REDOX CYCLE AGAINST ADRIAMYCIN-MEDIATED TOXICITY IN ISOLATED HEPATOCYTES.

Babson JR, Abell NS, Reed DJ
(c/o Reed) Dept. Biochemistry and Biophysics, Oregon State Univ., Corvallis, OR, 97331
Biochem Pharmacol; 30(16):2299-2304 1981

Incubation of isolated rat hepatocytes with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) resulted in the selective and extensive (greater than 90%) inactivation of glutathione reductase. BCNU also depleted intracellular glutathione by 70% but had no significant effect on cell viability or lipid peroxidation. Incubation of BCNU-treated hepatocytes with adriamycin (ADR) resulted in a decrease in cell viability concurrent with an increase in lipid peroxidation. These effects were not observed with untreated hepatocytes incubated with ADR. Glutathione depletion with diethylmaleate and incubation with ADR did not result in a significant decrease in cell viability or increase in lipid peroxidation. Incubation of BCNU-treated hepatocytes with ADR in the presence of exogenous alpha-tocopherol resulted in a significant amount of protection from ADR-mediated damage. (Author abstract) (47 Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

19. MODIFICATION OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RATS WITH INDUCERS OF THE CYTOCHROMES P-450.

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Dept. Pharmacology and Therapeutics, McGill Univ., Montreal, Quebec H3G 1Y6, Canada
Teratology; 24(1):1-11 1981

The chemotherapeutic agent cyclophosphamide (CP) may act as a carcinogen if it is enzymatically metabolized to reactive intermediates with alkylating, mutagenic, or cytotoxic effects, which activation is thought to be catalyzed by the cytochrome P-450 monooxygenase system. Phenobarbital (PB) induces the hepatic cytochrome P-450 that is involved in the activation of CP to both alkylating and mutagenic metabolites; beta-naphthoflavone (bNF) induces a different cytochrome P-450 and actually decreases the activation of CP by liver microsomes. Using rats pretreated with either PB or bNF, the activation of CP to mutagenic metabolites by enzyme fractions on day 13 of gestation was measured with the Ames test on Salmonella typhimurium TA1535 and teratogenicity was assessed in vivo by treatment of rats with CP on day 13 of gestation. CP was activated to mutagenic metabolites to the same extent (on a tissue wet wt basis) by enzyme fractions from maternal liver, kidney, and placenta, despite differences in cytochrome P-450 content, but fetal homogenates did not activate CP. PB pretreatment increased the liver cytochrome P-450 content 1.8-fold and the activation of CP by maternal liver microsomes 10-fold; however, PB did not alter the activation of CP by maternal kidney, by placenta, or by the fetus. PB pretreatment increased the teratogenicity of CP as measured by an increased incidence of malformed embryos or by decreased fetal wt. Pretreatment with bNF did not induce the hepatic cytochrome P-450 in the pregnant rat; did not change the activation of CP to mutagenic metabolites by liver, kidney, the placenta, or the fetus; and had no effect or decreased the teratogenicity of CP. These results suggest that the mother, rather than the fetus, is the site of PB activation; that the principal site of activation is the maternal liver; and that there is a correlation between the teratogenicity and mutagenicity of CP after induction by cytochrome P-450. (36 Refs)

20. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Kaneda S, Seno T, Takeishi K
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JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutag enic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved. (Author abstract) (31 Refs)

21. METABOLIC FATE OF N,N-DIPROPYLNITROSAMINE AND N,N-DIAMYLNITROSAMINE IN THE RAT, IN RELATION TO THEIR LACK OF CARCINOGENIC EFFECT ON THE URINARY BLADDER.

Suzuki E, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):552-561 1981

The metabolic fate of N,N-dipropylnitrosamine (DPN) and N,N-dipentyl(=diamyl)nitrosamine (DAN), which induce tumors principally in the liver and esophagus but not in the urinary bladder, was studied in the rat, in order to elucidate the reason for this lack of carcinogenicity to the urinary bladder in contrast with the butyl homolog, N,N-dibutylnitrosamine (DBN), a potent bladder carcinogen. The principal urinary metabolite of DPN was identified as the omega-oxidation product N-propyl-N-(2-carboxyethyl)nitrosamine. The (omega-1)-oxidation product N-propyl-N-(2-hydroxypropyl)nitrosamine and its glucuronic acid conjugate were also characterized as metabolites. The principal urinary metabolite of DAN was N-amyl-N-(2-carboxyethyl)nitrosamine, which was formed by metabolic shortening of the amyl chain by omega- and beta-oxidations according to the Knoop mechanism. Besides this, seven compounds oxidized at omega-, (omega-1)-, (omega-2)-, and (omega-3)-positions of one or both amyl chains were isolated and characterized, some of which were shown to be also present as the corresponding glucuronide. The metabolic pattern of DPN and DAN was compared with that of DBN, and the lack of carcinogenicity of the former N-nitrosamines to the urinary bladder of rats is discussed on the basis of their urinary metabolites. (Author abstract) (20 Refs)

22. RELEASE OF MUTAGENIC METABOLITES OF BENZO[A]PYRENE FROM THE PERFUSED RAT LIVER A FTER INHIBITION OF GLUCURONIDATION AND SULFATION BY SALICYLAMIDE.

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Chem Biol Interact; 36(2):167-177 1981

The role of glucuronide and sulfate conjugation in presystemic inactivation of benzo[a]pyrene (BP) metabolites was investigated with rat livers perfused with BP (12 u moles). Comparisons were made between metabolite profiles and mutagenicity of medium from perfusions with and without salicyclamide, a selective inhibitor of glucuronide and sulfate conjugation. After 4 hr perfusion in the presence of salicylamide, certain BP metabolites (diols, quinones, phenols, and metabolites more polar than BP-9,10-diol) were significantly increased at the expense of quinones and phenols in the glucuronide fraction. Mutagenicity of medium (detected by the Ames test, using tester strains TA98 and TA100) was low in perfusion without salicylamide. Mutagenicity detected with tester strain TA98 was significantly increased in perfusions with salicylamide. Involvement of glucuronidation in BP inactivation was also observed at the subcellular level when cofactors of glucuronidation were added to liver homogenates along with the NADPH regenerating system in the Ames test, BP mutagenicity was markedly decreased. Both the activation of BP to mutagenic metabolites and the inactivation of BP metabolites by glucuronidation was much more pronounced with liver homogenates from 3-methyl-cholanthrene-treated rats than with those from phenobarbital-treated animals or untreated controls. The results suggest an important role for glucuronidation and sulfation in the inactivation and elimination of polycyclic aromatic hydrocarbons. (Author abstract) (26 Refs)

23. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

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Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from those generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin

B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

24. POLYHALOGENATED BIPHENYLS AND PHENOBARBITAL: EVALUATION AS INDUCERS OF DRUG METABOLIZING ENZYMES IN THE SHEEPSHEAD, ARCHOSARGUS PROBATOCEPHALUS.

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Chem Biol Interact; 36(2):229-248 1981

Several doses of Aroclor 1254 (polychlorinated biphenyl (PCB) mixture), Firemaster FFl (polybrominated biphenyl (PBB) mixture), 2,2',4,4',5,5'-hexabromobiphenyl (HBB), 3,3',4,4',5,5'-hexachlorobiphenyl (HCB) and phenobarbital (PB) were administered to the marine fish sheepshead (Archosargus probatocephalus). The PCB and PBB mixtures caused induction of hepatic microsomal benzo[a]pyrene hydroxylase (AHH), 7-ethoxycoumarin O-deethylase (7-EC) and 7-ethoxyresorufin O-deethylase (ERF) activities, but not benzphetamine N-demethylase (BND), epoxide hydrolase (EH) or glutathione S-transferase (GSH-T) activities. This induction pattern is typical of that caused by polycyclic aromatic hydrocarbons (PAH) in fish and mammals or by tetrachlorodibenzo-p-dioxin (TCDD) in mammals. The extent of induction of AHH-activity and cytochrome P-450 content was higher when experiments were carried out in summer (water temperature 25 +-4 C) than in winter (water temperature 11 +-3 C). Firemaster FF1 (15 mg/kg) induced fish for at least 56 days in both summer and winter at which time the liver concentrations of PBB were in the ppm range. PCB concentrations in the ppm range have been found in fish from polluted lakes and seas, thus we may expect that environmental exposure to PCB is sufficient to induce hepatic mixed function oxidase (MFO) activities. The PCB isomer 3,3',4,4',5,5'-HCB, which induces the same spectrum of hepatic drug-metabolizing activities as TCDD and PAH in rats, had a broadly similar effect in the sheepshead. Another purified isomer 2,2',4,4',5,5'-HBB, which induces the same enzymes as PB in rats, had no effect on drug-metabolizing activities in sheepshead. PB was also without effect on sheepshead hepatic drug-metabolizing enzymes, although a typical narcotic effect was produced in PB-treated sheepshead. Our studies provide further evidence that drug-metabolizing activities in fish liver are readily induced by chemicals like TCDD or PAH, but we fail to demonstrate induction after treatment of sheepshead with inducers of the PB type. (Author abstract) (48 Refs)

25. REPAIR OF DNA ADDUCTS OF THE CARCINOGEN 15,16-DIHYDRO-11-METHYLCYCLOPENTA[A]PHENANTHREN-17-ONE IN MOUSE TISSUES AND ITS RELATION TO TUMOR INDUCTION.

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Cancer Res; 41(10):4115-4120 1981

The formation and repair of DNA adducts of the carcinogen, 15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one, have been studied in three mouse tissues, liver, lung, and skin. Following a single im dose of the carcinogen, DNA adduct formation was observed in all three tissues, the highest being found in liver DNA, the tissue resistant to tumor formation by this carcinogen. In skin and lung, the tissues which were susceptible to tumor formation, binding was approx one-half that found in liver. Detailed analysis by high-pressure liquid chromatography of the adducts formed in each of the three tissues revealed no major qualitative differences in the eight adduct peaks. In vivo removal of the labeled adducts was studied over a 14-day period following initial treatment, and adducts were analyzed at each time point by high-pressure liquid chromatography. In skin and lung, active removal of the major adducts could not be measured above the normal rate of DNA turnover. By contrast, in the liver, where the rate of DNA turnover was slower, adducts were removed relatively rapidly with a half-life of approx 2.5 days. Only one minor adduct present in both skin and liver was removed more rapidly than were the major adducts. The results suggest that the persistence of carcinogen-DNA adducts coupled with a relatively high rate of cell division may be related to tissue-specific carcinogenesis by this polycyclic ketone. (Author abstract) (33 Refs)

26. CHLOROETHANES: THEIR METABOLISM BY HEPATIC CYTOCHROME P-450 IN VITRO.

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Carcinogenesis; 2(8):697-702 1981

Hepatic microsomes were obtained from male Long-Evans rats. Microsome suspensions were exposed to 1,1,1-trichloroethane (111T), 1,1,2-trichloroethane (112T), or 1,1,2,2-tetrachloroethane (1122T). Levels of cytochrome P450 were measured, and metabolites of the chloroethanes were identified and quantified. The binding of chloroethanes was enhanced by the induction of cytochrome P-450 by phenobarbital (PB). It was not enhanced by the induction of cytochrome P-448 by beta-naphthoflavone (BNF). All three chloroethanes stimulated CO-inhibitable NADPH oxidation (CINO) by the hepatic microsomes. BNF induction decreased CINO for all three chloroethanes. PB induction increased CINO for 111T and 112T, but not for 1122T. CINO and metabolite formation were inhibited by CO, 2-diethylaminoethyl-2,2-diphenylvalerate (SKF-525A), and/or metyrapone. The results confirmed that all three chloroethanes were metabolized by cytochrome P-450. The metabolites of 111T, 112T, and 1122T were 2,2,2-trichloroethanol, monochloroacetate, and dichloroacetate, respectively. Proposed mechanisms for metabolism are described, with relationship to the relative mutagenicity and carcinogenicity of the three chloroethanes. (29 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

27. INCREASE OF T CELLS IN THE LIVER DURING HEPATOCARCINOGENESIS WITH N-2-FLUORENYLACETAMIDE IN RATS.

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Gan; 72(4):610-614 1981

The localization of thymus-derived lymphocytes (T cells) was investigated in rat liver by the immunofluorescence method during hepatocarcinogenesis with N-2-fluorenylacetamide. In the early stage of carcinogenesis, the number of T cells never increased significantly in livers in which hyperplastic liver nodules (population I) were seen. On the other hand, in the late stage of carcinogenesis, T cells extensively invaded hyperplastic nodules (population II) as well as hepatomas. According to the concept of cell-mediated immunity, hyperplastic nodules in the late stage might have a neoantigen(s) which evokes the response of T cells. Therefore, it may be concluded that populations I and II are biologically distinct lesions in spite of their histological identity. (Author abstract) (13 Refs)

28. PRIMARY LIVER CELL CARCINOMA COMPLICATING AUTOIMMUNE CHRONIC ACTIVE HEPATITIS.

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Dig Dis Sci; 26(8):694-699 1981

In a group of 50 patients seen with primary liver cell carcinoma over a period of 5 yr, 38 had cirrhosis. In four patients the cirrhosis was due to autoimmune chronic active hepatitis. None of the patients had markers of hepatitis B virus infection, but in three of the four, serum autoantibodies were present. Coexisting autoimmune disease was present in two. Corticosteroids induced remission in all patients, and the liver disease appeared quiescent at the time primary liver cell carcinoma developed. (Author abstract) (16 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

29. THE RELATIONSHIP BETWEEN TISSUE MORPHOLOGY IN EXPERIMENTAL LIVER CANCER AND SYSTEMIC ORGAN BLOOD FLOW: A STUDY BY SYSTEMIC AUTORADIOGRAPHY.

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Myakkangaku; 21(2):109-117 1981

The relationship between the histomorphological changes during the growth of experimental liver cancer induced by 3'-methyl-4-dimethylaminoazobenzen (3'-Me-DAB) and the changes in systemic organ blood flow determined by systemic autoradiography with 14C-dextran carboxyl was studied by determining the degree of blackening in vivo and unit tissue blood flow in vitro. The relation between the tissue profiles of hepatic tumors and their size was also studied. Morphological changes resulting from the development of experimental liver cancer were investigated in four stages. Namely, the lobule destruction stage (up to the 5th wk), the regeneration stage (from the 6th to the 7th wk), the redestruction stage (from the 8th to the 13th wk) and the tumor forming stage (in and after the 14th wk). Unlike human hepatocellular liver cancer, the tissues affected by hepatic tumors were classified into hepatocellular liver cancer, epithelial cellular cholangioma and mixed type carcinoma. With systemic autoradiography, only the kidney displayed excretion 60 sec later, other organs showing no changes. The blood flow in the livers of Donryu male rats determined for 23 wk after administration of 3'-Me-DAB showed a 5.25% decrease for the lobule destruction stage, a 21.54% increase for the regeneration stage, a 105.25% increase for the redestruction stage, a 13.51% decrease for the tumor forming stage and a 7.98% increase for the terminal stage. Autoradiography findings of the tumors could be classified into three groups. One showing remarkable increases in the degree of blackening, another showing a hive-shaped blackening arising from intra-tumoral increases and decreases in blackening and the rest showing a blackening of part of the surrounding area of the tumor accompanied by greatly reduced intra-tumoral blackening. In the in vitro study, the ratio of tissue blood flow between the tumoral and non-tumoral areas tumor region/surrounding region (T/S) ratio showed correlation with the size of the tumor. The av T/S ratio for hepatocellular liver cancer was 141.98%, that for mixed type carcinoma was 50.22% and that for epithelial cellular cholangioma was 25.02%. The T/S ratio decreased with the expansion of the tumor, regardless of its tissue type. (20 Refs) (In JPN)

30. IMMUNOHISTOCHEMICAL STUDIES OF ALPHA-FETOPROTEIN- AND ALBUMIN-CONTAINING CELLS IN THE LIVER DURING ONTOGENESIS AND THE EARLY STAGE OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE (3'ME-DAB) HEPATOCARCINOGENESIS.

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Kanzo; 22(2):254-265 1981

Single and simultaneous occurrence of alpha-fetoprotein (AFP) and albumin (ALB) in the liver of rat fetuses, neonatal rats and rats fed a 3'methyl-4-dimethylaminoazobenzene (3'Me-DAB) diet was studied by the peroxidase-labeled antibody method. In the very early stage of hepatocarcinogenesis, when maturation from oval cells to transitional cells began to occur, only AFP was found in the scant cytoplasm of transitional cells. In a more advanced stage, when maturation from oval cells to transitional cells and small hepatocytes occurred frequently, simultaneous presence of AFP and ALB was observed in those cells. When small hepatocytes assumed the appearances of hepatocytes, only ALB was found in them. By day 12 of gestation, AFP and ALB were already present in all hepatocytes. This tendency continued during the entire fetal life. After birth, AFP-containing cells gradually disappeared from the periphery of the hepatic lobe toward the central area. Finally, all hepatocytes contained only ALB. The fluctuation of AFP and/or ALB-containing cells in the early stage of 3'Me-DAB hepatocarcinogenesis was very similar to that of ontogenesis of rat liver. That is, the former retraced the process of ontogenic differentiation of the liver. (46 Refs) (In JPN)

31. CYTOPLASMIC EXPRESSIONS SEEN IN HEPATOCELLULAR CARCINOMA.

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Kanzo; 22(2):266-273 1981

The frequency and degree of occurrence of eight cytoplasmic expressions in carcinoma cells of minute and huge hepatocellular carcinoma (HCC) were determined. Fat accumulation, orcein-positive granules (but neither hepatitis B surface antigen nor copper-containing granules), iron stain-positive granules, and Mallory's hyaline were seen more frequently in minute HCC than in huge HCC (p less than 0.001), indicating that the expression-positive cells appear in the early stage of HCC and may be mostly replaced by negative cells in huge HCC. Bile plugs and globular hyaline, however, were frequently seen in huge as well as in minute HCC (p greater than 0.3), indicating that they are rather persistent cytoplasmic expressions of HCC throughout the entire course. Clear-cell transformation and ground-glass change of carcinoma cells were rarely seen, with no difference in frequency between the two types of HCC. (Author abstract) (24 Refs) (In JPN)

32. RAPID DEVELOPMENT OF LARGE NUMBERS OF ALPHA-FETOPROTEIN-CONTAINING 'OVAL' CELLS IN THE LIVER OF RATS FED N-2-FLUORENYLACETAMIDE IN A CHOLINE-DEVOID DIET.

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Gan; 72(4):479-487 1981

Fischer rats, fed 0.05% w/w N-2-fluorenylacetamide in a choline-devoid diet for 2 wk, developed a massive infiltration of the liver by small 'oval' cells. This occured rapidly 1 wk after feeding the diet for 2 wk. All of the rats fed the choline-devoid diet died within 5 wk, with massive oval cell infiltration of the liver. Although similar changes occurred in rats fed N-2-fluorenylacetamide in a choline-supplemented diet, the degree was much less. In rats fed a choline-devoid diet without N-2-fluoreny lacetamide, proliferation of hepatocytes, but not of oval cells, was observed. Because the carcinogen-enhancing effects of choline-devoid diets seem to exceed those of partial hepatectomy, such diets may work by causing changes distinct from those induced by partial hepatectomy. Many oval cells contain alpha-fetoprotein, and the rapid oval cell increase is associated with an exponential increase in serum alpha-fetoprotein concentration. These observations suggest that a cellular change, not an alteration of gene expression in parenchymal cells, is the primary cause of hyper-alphafetoproteinemia during the course of chemical carcinogenesis in rats. (Author abstract) (40 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

33. EARLY EVENTS DURING LIVER CARCINOGENESIS INVOLVING TWO CARCINOGEN:PROTEIN COMPLEXES.

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Cancer Res; 41(10):4039-4049 1981

This report describes the relationships between the levels of two principal carcinogen:protein complexes and histological alterations that occur during carcinogenesis in rat liver by three carcinogens. An intragastric tracer dose of N-[9-14C]-2-fluorenylacetamide interacts in normal rat liver to form the principal cytosolic 14C-carcinogen:protein complex (2S; M.W. 14,700). Continued ingestion of any of three hepatocarcinogens causes the marked loss of the 2S complex and the concurrent gain of a large-mol-wt carcinogen:protein complex (7.5S; M.W. approx 150,000) 48 hr following a dose of N-[9-14C]-2-fluorenylacetamide. The reciprocal changes in amounts of the two complexes have the following properties. The alterations occur early during hepatocarcinogenesis. In contrast to other reported early events, chemical carcinogen is directly involved. The two labeled fluorenyl proteins are the principal 14C-carcinogen:protein complexes in rat liver cytosol. Formation of the two complexes apparently involves activation of the carcinogen N-2-fluorenylacetamide. The reciprocal effects are brought on by the ingestion of any of the three hepatocarcinogens, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, and ethionine. The loss of the 2S complex was previously demonstrated to be associated with the loss of the 2S protein itself (14,700-daltons polypeptide) to which the carcinogen is bound. The rate of inversion in concentrations of the two complexes is apparently related to the susceptibility of the strain and sex of rat to the carcinogen; the greater the susceptibility the more rapid is the rate. The time of the max inversion coincides approx with the appearance of putative malignant lesions. Cessation of N-2-fluorenylacetamide ingestion results in the symmetrical reversal of the reciprocal changes in the levels of the two complexes. Liver regeneration follow ing partial hepatectomy brings about a moderate inversion of the levels of the two complexes, suggestive of the possibility that the cell proliferation associated with hepatocarcinogenesis may be casually related to the effects. Consistent with this possibility, the 2S protein has a mol wt like those of known polypeptide growth regulators. The effects on the 2S and 7.5S carcinogen:protein complexes are carcinogen group specific, inasmuch as the ingestion of any of three other types of liver carcinogens, namely, diethylnitrosamine,aflatoxin B, and thioacetamide, does not induce the reciprocal changes in the levels of the two complexes. The existence of such carcinogen group specificity suggests that chemical classes of carcinogens may be grouped on the basis of their common actions and effects on their target macromolecules. The generalizations to be derived from a classification of carcinogen group specificities seem likely to advance understanding of underlying events in chemical oncogenesis. (33 Refs)

34. DIFFERENCES OF EXPRESSION OF CYTOSKELETAL PROTEINS IN CULTURED RAT HEPATOCYTES AND HEPATOMA CELLS.

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Exp Cell Res; 134(2):345-365 1981

Cytoskeletal elements, enriched in intermediate-size filaments and insoluble in buffers of high salt concentrations and Triton X-100, were isolated from various cultures of rat hepatocytes and hepatoma cells, and their proteins were studied by one- and two-dimensional gel electrophoresis and immunofluorescence microscopy. The cells examined included several permanent cell lines (MH1C1, HTC, hepatoma 72/22, clone 12 from Gunn rat hepatocytes, and cell clones from normal rat hepatocytes), as well as freshly dissociated hepatocytes that were cultured and allowed to attach to substratum for increasing periods of time, beginning at 24 hr after removal of the liver from the animal. Filaments containing vimentin, which were not found in hepatocytes grown in liver tissue, were detected in most of the cultured hepatocytes and hepatoma cells, except in MH1C1 cells, and were shown to be newly synthesized during the first days of primary culture. Maintenance of expression of filaments containing proteins immunologically related epidermal prekeratin ('cytokeratins') was observed in all cells examined but HTC cells. Detailed comparison of the cytokeratin polypeptides present in various hepatocyte and hepatoma cell cultures showed that, in some of the cultured epithelial liver cells, cytokeratins are expressed which are identical with, or similar to, those of normal hepatocytes grown in the liver. On the other hand, differences in cytokeratin polypeptides were also found among different hepatocyte-derived cell cultures. Changes of expression of cytoskeletal proteins were found to occur even in cloned cell populations, and cells positive for certain cytokeratins could be seen next to other cells that were negative. The results demonstrate that profound changes of cytoskeletal composition, especially concerning intermediate filament protein patterns, can occur during culturing in vitro. Moreover, we show that intermediate filament protein patterns, can occur during culturing in vitro. Moreover, we show that different intermediate filament proteins can be expressed in different hepatocyte-derived cell cultures and that changes of cytoskeletal composition can occur in a given cell population, without obvious effects on cell growth rate and cell morphology. During culturing of hepatocytes and hepatoma cells, there seems to be a general tendency to induce the production of vimentin filaments as well as to maintain the production of cytokeratins similar to the hepatocyte-specific cytokeratins in liver tissue. However, the demonstrated exceptions speak against a role of these filament proteins as prerequisites for the growth of an epithelial cell in vitro. Rather, the presence of filaments containing certain cytokeratins and of desmosomes in epithelial cells growing in vitro seems to reflect the synthesis of specific differentiation markers which may be lost, independently, in some cells during culturing. (Author abstract) (56 Refs)

35. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

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Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideration of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

36. ALTERATIONS IN DRUG-METABOLIZING ENZYMES DURING FEEDING OF THE CARCINOGEN 2-AMINOANTHRAQUINONE.

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Toxicol Appl Pharmacol; 60(2):204-212 1981

Changes in enzymes which metabolize drugs during periods of feeding with 2-aminoanthraquinone (AAQ), at carcinogenic levels, were studied in young female Fischer 344 rats. Rats were fed 2% AAQ for 2, 4, 8 or 14 wk; after treatment, some were returned to the control diet. Some rats on the control diet were pair-fed with the AAQ group. At least four rats were available for each enzyme determination. Controls were fed ad libitum. Feeding AAQ increased liver content of cytochrome P-450, cytochrome b5, and increased NADPH-cytochrome c reductase activity as early as 2 wk. After 4 wk of AAQ, there was no change in azodye reductase, although an increase was observed in pair-fed controls. However, after 8 and 14 wk of AAQ, there was a significant increase in dimethylaminoazobenzene reductase. AAQ feeding also led to increased activities of benzo(a)pyrene hydroxylase, epoxide hydrolase, and alpha-naphthol-O-glucuronyl transferase. AAQ feeding beyond 4 wk increased the activities of N-demethylases, aniline hydroxylase and azo reductase. After the experimental period of AAQ feeding, the measured enzyme activities during the recovery period remained elevated in rats fed AAQ for 14 wk for 1 or 2 wk, and 2-4 wk in rats fed AAQ for 8 wk. (22 Refs)

37. THE SERUM PSEUDOCHOLINESTERASE ISOENZYMES IN THE ACUTE, CHRONIC AND NEOPLASTIC LIVER DISEASES. (THE EXPERIMENTAL AND CLINICAL STUDY).

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Acta Gastroenterol Latinoam; 11(1):125-132 1981

The study examined the contribution of the liver to serum pseudocholinesterase (SPC) and the behavior of its isoenzymes in the pathologic liver parenchyma in rats. Of the 32 liver patients 10 had severe or moderate acute viral hepatitis, 10 decompensated alcoholic cirrhosis with jaundice, ascites and edema, 12 tumor patients (4 primitive hepatic tumors: 3 cancers and 1 benign hepatoma, and 8 metastases). The eight normal controls were department personnel. The blood was removed from 10 rats (Wistar, 250 g), the liver perfused with saline, then homogenized and centrifuged. Five isoenzymes were found in the rat liver homogenates, in the serum four to five. In the comparative study of these animals was demonstrated that a certain percentage of SPC was of extrahepatic origin. In the normal human serum four to five isoenzymes were found, the SPC total activity was 2100-3800 av 2886 Units (U)/liter (l). The SPC was decreased in liver patients: acute viral hepatitis 470-2300 av 1312 U/l, cirrhosis 470-800 av 668 U/l, hepatomas 350-3000 av 1630 U/l, metastases 503-1640, av 1005 U/l. The isoenzyme one was significantly decreased in cirrhotics and had a double peak. The isoenzyme five was elevated in three patients with hepatomas. (18 Refs) (In SPA)

38. STUDIES ON UDP-N-ACETYLGLUCOSAMINE: ALPHA-MANNOSIDE BETA-N-ACETYLGLUCOSAMINYLTRANSFERASE OF RAT LIVER AND HEPATOMAS.

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Biochim Biophys Acta; 661(1):148-157 1981

When homogenates of rat liver and hepatomas were centrifuged at 78,000 x g, over 90% of liver N-acetylglucosaminyltransferase assayed with beta-galactosidase- and beta-N-acetylhexosaminidase-treated asialofetuin as acceptor was recovered in the particulate fraction, while as much as 24% of hepatoma transferase was in the supernatant fraction. The particulate transferase solubilized by 0.2% sodium deoxycholate emerged from a DEAE-cellulose column at 0.04 M NaCl (transferase A). The supernatant fractions from all the hepatomas tested contained a second N-acetylglucosaminyltransferase eluted from the column at 0.02 M NaCl (transferase B). Transferase B was absent from liver supernatant fraction. The activities of these transferases toward various acceptors and the effect of beta-N-acetylhexosaminidase on their products suggest that both transferases are uridine disphosphate-N-acetylglucosamine: alpha-mannoside beta-N-acetylglucosaminyltransferase. Although ovalbumin and glycopeptide V, which was isolated from pronase digest of ovalbumin, were good acceptors, transferase A utilized ovalbumin and glycopeptide V with apparent Km values of 0.44 and 0.33 mM, respectively, whereas the corresponding values for transferase B were 4.5 and 0.050 mM. (Author abstract) (37 Refs)

39. THE EFFECT OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE ON FOETAL RAT HEPATOCYTES IN CULTURE.

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Dept. Physiology, Univ. Western Australia, Nedlands, 6009, Western Australia

Eur J Cancer Clin Oncol; 17(7):743-752 1981

In hepatocyte cultures derived from 15-day and 19-day rat fetuses tyrosine aminotransferase accumulates during culture. In 15-day fetal hepatocytes enzyme is not detectable on day 1, whereas enzyme is already present in 19-day fetal hepatocytes at the same time. The effect of the hepatocarcinogen, 3'-methyl-4-dimethylaminoazobenzene (MDAB) on these two populations of differentiating hepatocytes is the subject of this study. This was undertaken to test the proposal that carcinogens may exert their effect on differentiating precursor cells. In cultures of 19-day fetal hepatocytes, accumulation of tyrosine aminotransferase is suppressed by MDAB whereas other liver enzyme markers examined, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, are not depressed. It is inferred from this result that hepatocytes that are about to initiate synthesis of tyrosine aminotransferase are prevented from doing so by the action of the carcinogen. In contrast, the synthesis of phosphoenolpyruvate carboxykinase by these cells which was initiated much earlier in development is unaffected. These findings would be consistent with the concept that carcinogens affect differentiating cells. In 15-day fetal hepatocytes, contrary to expectation, no effect of the hepatocarcinogen could be demonstrated. It is suggested that this may be due to the inability of the very immature hepatocytes to activate the hepatocarcinogen. In agreement with the biochemical data, the 19-day fetal hepatocytes but not the 15-day fetal hepatocytes display altered morphology when exposed to MDAB. (Author abstract) (17 Refs)

40. INDIRECT ALKYLATION OF CBA MOUSE LIVER DNA AND RNA BY HYDRAZINE IN VIVO. A POSSIBLE MECHANISM OF ACTION AS A CARCINOGEN.

Quintero-Ruiz A, Paz-Neri LL, Villa-Trevino S

(c/o Villa-Treviño) Departamento Investigacion, Division de Estudios, Superiores de la Facultad Medicina Universidad Autonoma de Chihuahua, Apart Postal 1506 Sucursal 'C' Chihuahua, Chihuahua, Mexico

JNCI; 67(3):613-618 1981

Treatment of inbred CBA mice with hydrazine sulfate, a liver carcinogen, plus [14C]formate or L-[methyl-14C]-methionine as a source of 'C1' units, produced [14C]7-methyl-guanine (7-MG) in liver DNA and RNA. This methylated guanine was identified by its chromatographic characteristics in three different systems: on Sephadex G10, on Dowex 50, and by paper co-chromatography with authentic 7-MG. Mice that received [14C]formate alone showed no 7-MG in their DNA or RNA. In addition, mice treated with L-[methyl-14C]methionine alone showed no 7-MG in their DNA. These results suggest that 'indirect' alkylation of nucleic acids is a mechanism of cancer initiation by hydrazine. (Author abstract) (20 Refs)

41. ABERRANT METHYLATION OF LIVER DNA IN RATS DURING HEPATOTOXICITY.

Barrows LR, Shank RC
(c/o Shank) Community and Environmental Medicine, Coll. Medicine, Univ. California at Irvine, Irvine, CA, 92717
Toxicol Appl Pharmacol; 60(2):334-345 1981

Aberrant methylation of liver DNA as a response to hydrazine was studied. Male Fischer rats were given hydrazine (60 or 90 mg/kg body wt) by intubation. Liver DNA was analyzed using four high-pressure liquid chromatography methods, a paper chromatography method, and UV absorption spectrometry. Hepatotoxic DNA products were identified as 7-methylguanine (7MG) and O6-methylguanine (O6MG). Administration of [methyl-3H]methionine simultaneously with hydrazine produced labeled 7MG and O6MG, indicating that methylation of DNA was mediated by methionine and S-adenosylmethionine. Aberrant methylation of DNA was also produced by administering ethanol (5 g/kg) or carbon tetrachloride (1 g/kg). Evidently such methylation may be a nonspecific response by the liver to chemical injury. (25 Refs)

42. ON THE PECULIARITIES OF METHYLATION OF DNA OF DIFFERENT TISSUES OF RAT'S FETUS AND MATERNAL ORGANISM AFTER 1,2-DIMETHYLHYDRAZINE TREATMENT.

Likhachev AYa, Petrov AS
N. N. Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR
Vopr Onkol; 27(7):71-73 1981

A high rate of DNA methylation in the liver and large colon mucosa was registered 6 hr after dimethylhydrazine (SDMH) treatment of rats with 19-day gestations. However, in fetal liver, a low concentration of methylated guanine (7-methyl guanine) derivatives was found, while in large colon and brain, these substances were not detected at all. It is suggested that the resistance of embryonal tissues to the transplacental effect of SDMH is due to the underdeveloped enzymatic system of the fetus. (Author abstract) (8 Refs) (In RUS)

43. FAILURE TO DISCRIMINATE INITIATION FROM PROMOTION OF LIVER TUMORS IN A LONG-TERM STUDY WITH THE PHENOBARBITAL-TYPE INDUCER ALPHA-HEXACHLOROCYCLOHEXANE AND THE ROLE OF SUSTAINED STIMULATION OF HEPATIC GROWTH AND MONOOXYGENASES.

Schulte-Hermann R, Parzefall W
Institut fur Toxikologie und Pharmakologie, Pilgrimstein 2, 335 Marburg, W. Germany
Cancer Res; 41(10):4140-4146 1981

The compound alpha-hexachlorocyclohexane (alpha-HCH) was administered po to female Wistar rats for periods of up to 33 mo; doses were 20 mg/kg/day, 200 mg/kg every 2nd wk, or 420 mg/kg every 3rd wk. Increases of liver size, DNA, RNA, and protein (by 50 to 100%) and of drug-metabolizing enzyme activities (up to 300%) observed previously after single doses of alpha-HCH were found to persist after approx 1/3, 1, and 2 yr of treatment. At 1 and 2 yr, DNA synthesis was measured by [3H]thymidine uptake and was no higher than in controls. All changes regressed upon withdrawal of alpha-HCH after 1 yr of treatment. These findings provide no evidence to suggest a protracted development of toxicity or of growth autonomy in the majority of liver cells. Foci of altered cells, neoplastic nodules, and in 2 animals hepatocellular carcinoma were detected histologically in the livers of 24 of 34 treated rats. In livers of 10 of 22 untreated control rats, foci of altered cells developed 'spontaneously' between 12 and 34.5 mo. If neoplastic lesions were induced by a single dose of diethylnitrosamine, 75 or 150 mg/kg, subsequent treatment with alpha-HCH led to the appearance of hepatocellular carcinoma within 7 mo. Altogether, hepatocellular carcinomas were found in 18 of 21 rats treated with both agents but in only 3 of 26 animals treated with diethylnitrosamine alone. The results show that determination of tumor numbers alone in a long-term animal experiment does not allow one to decide whether alpha-HCH (and similar 'xenobiotic inducers') is an initiating carcinogen or merely promotes tumorigenesis from 'spontaneous' lesions. Our findings support the latter possibility by the failure to detect evidence suggesting initiating potential of alpha-HCH, by the enhanced mitotic response to alpha-HCH in foci of altered cells as reported elsewhere, and by the observation of a permanent stimulatory action on liver growth during prolonged exposure to alpha-HCH. (Author abstract) (46 Refs)

44. COMPARISONS OF THE EFFECTS OF CHEMICAL CARCINOGENS IN MIXED CULTURES OF RAT HEPATOCYTES AND HUMAN FIBROBLASTS.

Strom S, Kligerman AD, Michalopoulos G
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Carcinogenesis; 2(8):709-715 1981

Human male diploid fibroblasts (strain GM 3468) and parenchymal hepatocytes from male Sprague Dawley rats were treated separately and in mixed cell cultures with benzo[a]pyrene (BP), diethylnitrosamine (DEN), or 2-acetylaminofluorene (AAF). Fibroblast DNA was prelabeled with 5-bromo-2'-deoxyuridine. After exposure to the carcinogens, fibroblast and hepatocyte DNA was analyzed for unscheduled DNA synthesis (UDS). Fibroblast and hepatocyte DNA from mixed cultures was separated by isopycnic centrifugation in neutral cesium chloride. The hepatocarcinogens DEN and AAF produced increased UDS in hepatocytes, but not in fibroblasts, either separately or in mixed cultures. BP, a non-hepatocarcinogen, produced more UDS in in fibroblasts than in hepatocytes in mixed cultures. More BP was bound to fibroblast DNA than to hepatocyte DNA. BP bound to DNA from cultures of fibroblast alone was about 30% of that bound to fibroblast DNA from mixed cultures. BP produced no UDS in fibroblast in the absence of hepatocytes. Evidently the hepatocytes activated the UDS-promoting capacity of BP, which then was passed to the fibroblasts. The results obtained with BP, DEN, and AAF correspond to previous in vivo observations of the tissue-specific carcinogenicity of the three agents. The possibility that intercellular distribution may play a role in carcinogenic effects is indicated. (37 Refs)

45. DIFFERENTIAL SENSITIVITY OF NORMAL AND CHEMICALLY TRANSFORMED EPITHELIAL CELLS TO CHOLERA TOXIN.

Niles RM, Loewy B, Krah D
Dept. Biochemistry, Boston Univ. Sch. Medicine, Boston, MA, 02118
Cancer Res; 41(10):4075-4079 1981

We have been studying the regulation of growth by cyclic AMP and other factors in untransformed (K16) and chemically transformed (W8) rat liver epithelial cells. Initially, we found that 8-bromocyclic adenosine 3':5'-monophosphate was a more potent inhibitor of cell replication in K16 than in W8 cells. In addition, the phosphodiesterase inhibitor 1-methyl-3-isobutylxanthine (MIX) caused marked growth inhibition in K16 but not in W8 cells. Through the use of cholera toxin (CT) with or without MIX, we elevated intracellular cyclic AMP levels in a quantifiable fashion. With CT alone or combined with MIX, we observed a dose-dependent morphological change in W8 cells, which consisted of extensive 'process' formation. K16 morphology was not altered at any concentration of CT +- MIX tested. K16 cell growth was only marginally inhibited by CT alone, but markedly inhibited by CT plus MIX. W8 cell growth was moderately inhibited by CT alone or combined with MIX. Analysis of cyclic AMP levels revealed that, at all concentrations of CT +- MIX and at all time periods tested, W8 cells produced significantly more cyclic AMP than K16 cells. It appears that morphological changes and growth inhibition are not necessarily linked and that MIX may inhibit K16 cell replication by means other than its ability to increase intracellular cyclic AMP levels. (Author abstract) (23 Refs)

46. EFFECTS OF VARIOUS METABOLIC INHIBITORS ON LIPOPEROXIDATION BY HOMOGENATES OF NORMAL, REGENERATING AND HEPATOMATOUS RAT LIVER AND BY HEPATOMA CELLS.

Agostini C
Centro Studi Patologia Cellulare del C.N.R., Instituto di Patologia Generale dell'Universita di Milano, Via Mangiagalli 31, 20133-Milano, Italy
Res Commun Chem Pathol Pharmacol; 33(3):563-566 1981

Lipoperoxidation by rat liver homogenates increases after in vivo administration of carbon tetrachloride, colchicine and cycloheximide. In vivo lipoperoxidative action was found for ADP/Fe+++, ethionine and glucosamine. No lipoperoxidation was elicited by hepatomous liver or by hepatoma cells. (Author abstract) (18 Refs)

47. EFFECT OF BENZO(A)PYRENE AND ITS NONCARCINOGENIC ANALOG 1,2-BENZOPYRENE ON NA,K-ATPASE ACTIVITY OF HOMOGENATES OF VARIOUS MOUSE ORGANS AND OF MEMBRANE PREPARATION FROM RAT HEART.

Mustafin AM, Kim SCh
Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR
Biull Eksp Biol Med; 91(7):76-77 1981

The effect of benzo(a)pyrene (BP) and its noncarcinogenic analog 1,2-benzopyrene (1,2-BP) on Na, K-ATPase activity was studied in homogenates of albino mice lungs, stomach, and liver. BP caused significant inhibition of enzyme activity in the lungs and in the stomach; the inhibitory effect of 1,2-BP was less pronounced. Both BP and 1,2-BP did not inhibit the enzyme activity of liver homogenate and activity of Na ,K-ATPase from the membranes of rat heart. (5 Refs) (In RUS)

48. BIOLOGICAL ACTIVITY OF CHALONES ISOLATED FROM NORMAL AND REGENERATING LIVER.

Ketlinskii SA, Parfenova EV
Lab. Experimental Histology, Inst. Experimental Medicine, Leningrad, USSR
Biull Eksp Biol Med; 91(7):96-98 1981

To evaluate the mechanism of the disappearance of the biological activity of chalones, random-bred hepatectomized rats were inoculated with chalones isolated from normal and regenerating liver. Chalones isolated 22 hr or 28 hr after hepatectomy failed to inhibit mitotic activity of the hepatocytes, but provided a 55% inhibition of DNA synthesis. It was suggested that the loss of chalone activity was associated with the changes in the competitive relationship between the inhibitors and stimulants of proliferation. (6 Refs) (In RUS)

49. DIFFERENTIATION OF THE MECHANISMS OF ONCOGENICITY OF 1,4-DIOXANE AND 1,3-HEXACHLOROBUTADIENE IN THE RAT.

Stott WT, Quast JF, Watanabe PG
Toxicology Res. Lab., Dow Chemical U.S.A., Midland, MI, 48640
Toxicol Appl Pharmacol; 60(2):287-300 1981

Two tumorigenic agents, 1,4-dioxane (DX) and 1,3-hexachlorobutadiene (HCBD) were compared to the known mutagen dimethylnitrosamine (DMN) to determine whether their actions were by a genetic or nongenetic mechanism. Male Sprague Dawley rats were given tumorigenic doses of DX in drinking water (0, 10 or 100 mg/kg/day for 11 wk), HCBD by gavage (0, 0.2, or 20 mg/kg/day for 3 wk), or DMN by gavage (3 mg/kg/day for 3 wk). Other groups of rats were given single doses of DX (10, 100, 1,000 mg/kg), HCBD (0.2, 20 mg/kg), or DMN (3 mg/kg) by gavage. DX produced no genotoxic effects at tumorigenic doses. A single large dose produced no alkylation of DNA or increase in DNA repair. Repeated high doses of DX were hepatotoxic. HCBD produced a minor genotoxic effect compared with DMN. DNA repair in renal tissue was increased 1.27-1.54-fold by HCBD (20 mg/kg); DNA alkylations occurred at the rate of 0.78 per 10(6) nucleotides. No mutations were produced in the Ames' bacterial mutagenesis assay. HCBD produced renal cytotoxicity. Apparently DX induces tumors by a nongenetic mechanism. HCBD acts primarily in a nongenetic way, but is weakly genotoxic. Risk from either compound is likely only at cytotoxic doses. (34 Refs)

REVIEWS AND OTHER RELATED STUDIES

50. BIOLOGIC MARKERS IN CANCER DIAGNOSIS AND TREATMENT.

Holyoke ED, Block GE, Jensen E, Sizemore GW, Heath H, Chu TM, Murphy GP, Mittelman A, Ruddon RW, Arnott MS
Roswell Park Memorial Inst., Buffalo, NY
Curr Probl Cancer; 6(2):68pp. 1981

The clinical use of tumor markers in detecting and monitoring the progress of tumor treatment is reviewed. In breast cancer treatment, the intracellular presence of an estrogen receptor protein identifies those tumors that are hormone-dependent and thus capable of responding to hormone manipulation (therapy). The presence or absence of progesterone receptors has not proved clinically useful. Calcitonin has been shown to be useful as a biological marker of medullary thyroid carcinoma; there are numerous tests and measurements for it, such as pentagastrin injection, long calcium infusion, short calcium infusion, and ethanol ingestion. The measurement of elevated levels of prostatic acid phosphatase by such techniques as radioimmunoassay, counterimmunoelectrophoresis, solid-phase immunofluoroassay, and solid-phase immunoadsorbent assay offers a method of identifying patients in the early stages of prostate cancer and monitoring the efficacy of treatment. The detection of certain 'tumor-associated antigens' such as alpha-fetoprotein, tissue peptide antigen, fetosulfoglycoprotein, pancreatic oncofetal antigen, and carcinoembryonic antigen (CEA) have various applications in screening, diagnosis, and staging of cancer; CEA may be of value in monitoring the adequacy of therapy and the treatment of advanced disease and in detecting persistent progressive disease in patients with colon cancer; alpha-fetoprotein is sensitive and specific enough for hepatocellular cancer to be of clinical use in this disease. Various protein degradation products are associated with tumors; plasminogen-dependent protease activity is one of the most likely candidates for a proteolytic activity as a tumor marker substance. Measurements of plasminogen activator, plasmin-derived products, and plasma protein degradation products in serum and/or urine are being investigated for their utility as tumor markers. Measurements of tissue aryl hydrocarbon hydroxylase may help to identify populations at risk of cancer resulting from chemical carcinogenesis. (245 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Diviao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

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6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

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Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

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IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
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10. PANCREATIC CANCER.

Conn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

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Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.

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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
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ACS Symp Ser; 160:197-215 1981

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Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

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Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

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Usp Sovrem Biol; 91(3):409-418 1981
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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

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25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

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J Gen Virol; 54(part1):1-8 1981

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26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
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27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

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Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

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Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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ORGAN SITE CARCINOGENESIS

Liver

SERIES CK16 No. 82/02

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. MORTALITY AMONG RUBBER WORKERS. III. CAUSE-SPECIFIC MORTALITY, 1940-1978.

Delzell E, Monson RR

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115

JOM; 23(10):677-684 1981

This report describes mortality occurring between 1940 and mid-1978 among 29,087 men and women employed in a rubber plant for at least 2 yr. Mortality patterns for the period July 1, 1974, to July 1, 1978, were compared to previously published findings for January 1, 1940, through June 30, 1974. Expected numbers of deaths were based on U.S. general population mortality data. There were excess d eaths from bladder cancer and leukemia among white male union members during both follow-up periods. During recent follow-up of white male union members employed for at least 5 yr, there were excesses in deaths from three additional cancers: esophageal cancer (11 observed/4.8 expected), biliary and liver cancer (6 observed/3.3 expected) and lymphoma and multiple myeloma (14 observed/5.8 expected). Evidence from other studies of rubber workers suggests that observed excesses in deaths from bladder cancer and leukemia are related to workplace exposures. The present findings suggest that occupational exposures etiologically relevant to these diseases may not have been reduced in recent yr or that sufficient time has not elapsed for such reductions to result in decreased mortality. Further investigation is required to clarify the contribution of occupational factors to observed excesses in deaths from cancers of the esophagus and the biliary passages and liver and from lymphoma and multiple myeloma. (Author abstract) (26 Refs)

2. CANCER MORTALITY OF A GROUP OF CANADIAN WORKERS EXPOSED TO VINYL CHLORIDE MONOMER.

Theriault G, Allard P

Dept. Social and Preventive Medicine, Sch. Medicine, Laval Univ., Ste-Foy, Quebec, Canada

JOM; 23(10):671-676 1981

The present study was undertaken to find out whether there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than 5 yr was compared with that of 870 workers from the same company who had not been exposed to VCM. The relative risk for digestive cancer was significantly higher than 1 (6.25, confidence interval 2.69 to 14.52) in the exposed group. The standardized mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 p less than 0.01) than that of the general population. No other cancer was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung cancer and VCM exposure, if present, is indeed rather small. (Author abstract) (25 Refs)

3. MALIGNANT TUMOURS IN MOZAMBICAN AFRICANS WITH SPECIAL REFERENCE TO PRIMARY LIVER CARCINOMA.

Bijlsma F

Academisch Ziekenhuis Universiteit van Amsterdam, Pathologisch-Anatomisch Laboratorium, Binnen Gasthuis, Amsterdam, The Netherlands

Trans R Soc Trop Med Hyg; 75(3):451-454 1981

The relative frequency of malignant disease as diagnosed by autopsy, biopsy, or cytology in Mozambican Africans during 1977 was compared with similar data from the period 1956-1970. The most striking feature was the steady decrease of primary liver carcinoma, mainly hepatocellular carcinoma, in male African patients: the relative frequencies were 51.8% in 1956-61, 52.9% in 1961-65, 50.4% in 1965-66, 45.6% in 1966-70, and 35.3% in 1977. This tendency was not noted among female African patients; the relative frequency figures for primary carcinoma of the liver fluctuated around 20% (20.7% in 1956-61 to 18.4% in 1977). The relative frequencies of other malignancies remained relatively constant over the yr 1977. Assuming an unchanging high incidence of viral hepatitis, liver cirrhosis, and food contamination by aflatoxin, the decrease in the frequency of liver carcinoma in men cannot be explained. (9 Refs)

4. LIVER TUMOURS IN PREGNANCY, FOLLOWING PREVIOUS INTAKE OF HORMONAL CONTRACEPTIVES.

Pietsch P, Petermann J, Zipprich B, Schwesinger G, Kagel KO

Universitats-Frauenklinik, Wollweberstr. 1, DDR-2200 Greifswald, E. Germany

Zentralbl Gynaekol; 103(13):772-780 1981

Liver tumors developed in two women during pregnancy which followed discontinuation of hormonal contraception. Liver cell adenoma developed in a secundipara, 24 yr of age, and its rupture during puerperium led to death by bleeding, after surgical intervention had failed. Hepatocellular carcinoma was recorded from a secundipara, 22 yr of age, and surgically treated, following premature delivery. Problems of diagnosis and the need for interdisciplinary cooperation are discussed and compared with literature data. The pathogenesis of liver tumors in the wake of exogenous hormone inflow and in the context of subsequent pregnancy is another topic of discussion. (Author abstract) (33 Refs) (In GER)

5. NEOPLASIA AND HORMONAL CONTRACEPTION.

Huggins GR

Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104

Clin Obstet Gynecol; 24(3):903-925 1981

The relationships between use of oral contraceptives and neoplasia are reviewed. Problems of investigation include lack of suitable animal models, lag time following exposure to carcinogens before development of overt malignancy, low incidence of malignancies in young women, and the wide range of factors influencing neoplasia. Investigative methods include case reports, disease rates and trends, case comparisons, and cohort studies. Breast disease is discussed with respect to the preclinical phase of breast cancer, breast cancer and chronic mastitis, the estradiol hypothesis, and the relationships between oral contraceptive use and benign and malignant breast disease. The relationships of oral contraceptives to liver tumors, pituitary tumors, endometrial hyperplasia, cervical neoplasia, ovarian disease, and choriocarcinoma are evaluated based on current published data. (56 Refs)

TUMOR INDUCTION IN ANIMALS

6. COMPARISON OF THE CARCINOGENICITY OF METHYLAZOXYMETHANOL-BETA-D-GLUCOSIDURONIC ACID IN CONVENTIONAL AND GERMFREE SPRAGUE-DAWLEY RATS.

Laqueur GL, Matsumoto H, Yamamoto RS
(c/o Matsumoto) Dept. Agricultural Biochemistry, Univ. Hawaii, 1800 East-West Rd., Honolulu, HI, 96822
JNCI; 67(5):1053-1055 1981

Methylazoxymethanol-beta-D-glucosiduronic acid (MAM-GlcUA) was administered to young adult male Sprague-Dawley rats by oral and ip routes. Most neoplasms developed in rats that had received the compound po. The most prevalent site for the neoplasms was the intestinal tract, predominantly the colon. Comparatively fewer tumors occurred in the liver and kidneys. Germfree rats did not develop tumors when MAM-GlcUA was administered either po or ip. (Author abstract) (9 Refs)

7. COMPARATIVE CARCINOGENICITY OF TWO ISOMERS OF NITROSO-2,6-DIMETHYLMORPHOLINE IN GUINEA PIGS.

Lijinsky W, Reuber MD
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Lett; 14(1):7-11 1981

The carcinogenic effectiveness of the cis and trans isomers of nitroso-2,6-dimethylmorpholine (Me2NMOR) in male guinea pigs was compared. Twenty animals received cis Me2NMOR in oil by gavage at a concentration of 10.5 mg/ml at a dose of 0.2 ml 2x/wk for 30 wk. The other group of 20 animals received trans Me2NMOR in oil by gavage at a concentration of 5.3 mg/ml at a dose of 0.2 ml 2x/wk for 30 wk. A the end of 105 wk, the cis group had 2 surviving animals while the trans group had 7. There were 17 tumor-bearing animals in the cis group and 2 in the trans group. The major site of tumor induction in the cis group was the liver: 16 animals had liver tumors; hepatocellular carcinomas or cholangiocarcinomas; most animals had two tumor types, several had all three types. There were metastatic hemangiosarcomas in five animals, metastatic hepatocellular carcinoma in two, and metastatic cholangiocarcinoma in one. There were also significant numbers of tumors of the lung and adrenal cortex, and other types of tumor. None of these tumors were seen in the animals treated with the trans isomer nor in untreated guinea pigs of the same strain. The disparate results with the two Me2NMOR isomers in rats as previously reported and in guinea pigs suggest that the mechanisms of activation in the two species might be different. (9 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

8. INHIBITION IN VIVO OF THE FORMATION OF ADDUCTS BETWEEN METABOLITES OF BENZO(A)PYRENE AND DNA BY BUTYLATED HYDROXYANISOLE.

Anderson MW, Boroujerdi M, Wilson AE
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Cancer Res; 41(11,part1):4309-4315 1981

Antioxidants have been shown to inhibit the carcinogenic effects of a variety of chemical carcinogens. For example, the phenolic antioxidant butylated hydroxyanisole (BHA) has been shown to be a potent inhibitor of benzo(a)pyrene (BP)-induced neoplasia in mouse lung and forestomach. The objective of the present study was to determine whether or not BHA, under conditions known to result in inhibition of BP-induced neoplasia, affects the formation of BP metabolite:DNA adducts. Following po administration of a carcinogenic dose of [3H]BP to A/HeJ mice, radioactivity was detected in the DNA of both lung and liver. Analysis of the deoxyribonucleosides by high-pressure liquid chromatography showed that the major adduct in both tissues cochromatographed with the (+-)-7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was 10 to 15% of the BPDEI adduct in both lung and liver. Another adduct, possibly derived from BP phenol(s), was also detected in lung and was 10 to 20% of the BPDEI adduct. Treatment of animals with BHA decreased the amount of the BPDEI adduct in the lung and the liver approx 55 and 75%, respectively. The decrease in the amount of this adduct in the lung appears to correlate with the inhibition of pulmonary adenoma formation. Thus, BHA appears to inhibit BP-induced pulmonary adenoma formation by inhibiting the amount of the BPDE:DNA adducts formed in lung. Possible mechanisms by which BHA treatment inhibits the formation of BPDE:DNA adducts are discussed. (Author abstract) (44 Refs)

9. EFFECT OF PHENOBARBITAL PRETREATMENT ON THE TOXICITY AND METABOLISM OF 2,4-DIAMINOANISOLE.

Ruchirawat M, Grantham PH, Benjamin T, Weisburger EK
(c/o Weisburger) Lab. Carcinogen Metabolism, Public Health Service, NCI, NIH, Dept. Health and Human Services, Bethesda, MD, 20205
Biochem Pharmacol; 30(19):2715-2718 1981

The effects of phenobarbital (PB) on the acute toxicity, macromolecular binding, disposition, and metabolism of 2,4-diaminoanisole (2,4-DAA) were studied in young male Fischer rats. At 5 and 24 hr after ip injection of [14C]-2,4-DAA, the highest concentration in control and PB-pretreated animals occurred in the kidney. Lower levels were found in the liver, spleen, lung, heart, and testis, respectively. The higest concentration of 2,4-DAA bound to tissue macromolecules was found in the kidney, followed by the liver, spleen, lung, heart, and testis, respectively. Concentrations of bound materials at 24 hr were approx half of those observed at 5 hr. Pretreatment with PB significantly increased binding, but only in the liver and kidney and not in other organs. In control rats, who received equal vol of NaCl and [14C]-2,4-DAA, 31% of the 14C dose was found in the urine in 5 hr, and 69% by 24 hr. In PB-pretreated rats, the rate of excretion of radioactivity was somewhat faster than that of the control animals: 42% of the radioactivity was in the urine at 5 hr. No difference in the excretion of total radioactivity or of the radioactivity in each fraction was observed between the PB-pretreated and control groups at the 24 hr period. The high pressure liquid chromatography separation of the five known metabolites of 2,4-DAA in control and PB-pretreated rats is described. The acute toxicity of 2,4-DAA was increased by PB treatment as evidenced by a change in the LD50 dose from 116 mg/kg to 97 mg/kg in the PB-pretreated rats. The mechanism and implications of the PB-related effects on 2,4-DAA metabolism are discussed. (14 Refs)

10. EFFECTS OF PHENOBARBITAL PRETREATMENT ON THE METABOLISM AND TOXICOKINETICS OF AFLATOXIN B1 IN THE RHESUS MONKEY.

Wong ZA, Wei CI, Rice DW, Hsieh DP
(c/o Hsieh) Dept. Environmental Toxicology, Univ. California, Davis, CA, 95616
Toxicol Appl Pharmacol; 60(3):387-397 1981

Five male rhesus monkeys were treated with phenobarbital (PB: 15 mg/kg, 2 x/day) for 1 wk prior to administration of aflatoxin B1 (AFB1: 0.1-1.0 mg/kg, iv). PB pretreatment enhanced the in vitro conversion of AFB1 to aflatoxin Q1 and aqueous metabolites in monkey liver. Although PB did not appreciably alter the rate or vol of AFB1 distribution in vivo, it reduced plasma levels of total aflatoxins, AFB1, and the toxic metabolite aflatoxin M1 (AFM1). Decreased AFM1 levels and increased levels of less toxic water-soluble metabolites were found in the urine of PB-treated monkeys. These findings demonstrated that increased hepatic AFB1 metabolism results in elimination and circulation of less toxic, less mutagenic, and highly excretable metabolites. (49 Refs)

11. 1,2-DIMETHYLHYDRAZINE-INDUCED CHANGES IN HEPATIC, SMALL INTESTINAL, AND COLONIC MUCOSAL CYTOCHROMES P-450 AND B5 OF RATS FED CITRUS PULP OR WHEAT BRAN.

Smith-Barbaro P, Hanson D, Reddy BS
Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Drug Metab Dispos; 9(5):487-488 1981

A 3-mo feeding study showed that dietary fiber and the carcinogen 1,2-dimethylhydrazine interacted to alter hepatic and extrahepatic levels of cytochromes P-450 and b5 in liver, and small intestine and colon mucosa of male F344 rats. (16 Refs)

12. BETA-NAPHTHYLISOTHIOCYANATE-INDUCED ALTERATIONS IN HEPATIC DRUG METABOLISM AND LIVER MORPHOLOGY.

Leonard TB, Popp JA, Graichen ME, Dent JG
Chemical Industry Inst. Technology, P.O. Box 12137, Research Triangle Park, NC, 27709
Toxicol Appl Pharmacol; 60(3):527-534 1981

The effects of continuous feeding with beta-naphthylisothiocyanate (BNIT: 0.022%, 0.047%, or 0.1% of diet for 4 wk) on liver histology and hepatic enzymes were studied in male Charles River F-344 rats. Rats fed 0.1% BNIT developed multifocal granulomatous inflammatory lesions, but the lesions did not alter SGPT or serum bilirubin levels. BNIT treatment resulted in a dose-dependent increase in hepatic cytochrome P-450, benzphetamine-N-demethylase, and ethoxycoumarin-O-deethylase activity. BNIT also stimulated DT-diaphorase activity, but it did not alter epoxide hydrolase activity assayed with benzo(a)pyrene-4,5-oxide or styrene oxide as substrates. These effects contrast markedly with those of alpha-naphtylisotiocyanate, which also inhibits chemically induced hepatocarcinogenesis. Stimulation of mixed-function oxidases and DT-diaphorase may be a factor in the anticarcinogenic action of BNIT. (36 Refs)

13. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

Kaufmann WK, Kaufman DG, Rice JM, Wenk ML
(c/o D. Kaufman) Dept. Pathology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed after 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extrahepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

14. ROLES OF 2-HALOETHYLENE OXIDES AND 2-HALOACETALDEHYDES DERIVED FROM VINYL BROMIDE AND VINYL CHLORIDE IN IRREVERSIBLE BINDING TO PROTEIN AND DNA.

Guengerich FP, Mason PS, Stott WT, Fox TR, Watanabe PG
Dept. Biochemistry, Center Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 41(11,part1):4391-4398 1981

The metabolism of [1,2-14C]vinyl bromide (VBR) to products irreversibly bound to DNA and protein was examined in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes. A role for cytochrome P-450 was confirmed using inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VBR metabolism does not appear to be either of the major isozymes induced by phenobarbital or beta-naphthoflavone, as determined by induction, reconstitution, and antibody inhibition studies. 2-Bromoethylene oxide and 2-bromoacetaldehyde, suspected metabolites of VBR, were synthesized and found to be substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. These enzymes were used to probe the roles of the two possible metabolites in the irreversible binding of products of VBR to protein and DNA. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VBR metabolites to protein in microsomal incubations. Epoxide hydrolase was effective in inhibiting the binding of VBR or vinyl chloride metabolites to calf thymus DNA added to such systems, but alcohol dehydrogenase was not. Similar results were obtained for binding of VBR metabolites to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo[1,2-14C]acetaldehyde to protein but not DNA. Binding of vinyl chloride and VBR metabolites to protein was blocked by reduced glutathione, but binding to DNA was not. These results are consistent with the view that 2-haloethylene oxides are the major alkylating agents bound to DNA, and 2-haloacetaldehydes are the major alkylating agents bound to proein in these experimental systems. Studies with labeled 2-bromoacetaldehyde indicate that the slow kinetics of DNA binding by this compound is responsible in part for this phenomenon. Studies with isolated rat hepatocytes suggest that a significant portion of the total and reactive metabolites are able to leave these cells. In these systems, binding of metabolites of vinyl chloride to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase, implying that, as targets farther away from sources of reactive species are considered, the stabilities of these species become more important for reaction with nucleophilic sites. (Author abstract) (36 Refs)

15. DIFFERENTIAL EFFECT OF SEVERAL INDUCERS ON HEPATIC AND MAMMARY BENZO(A)PYRENE METABOLISM IN RAT AND HAMSTER.

Gingell R, Weber A, Ilacqua V, Van de Walle C, Hertzog P
Shell Development Co., Westhollow Res. Center, P. O. Box 822, Houston, TX, 77001
Drug Chem Toxicol; 4(2):101-112 1981

The ability of female Sprague Dawley rat and Syrian golden hamster mammary microsomes, as compared with the liver, to metabolize benzo(a)pyrene (BP) was examined in an attempt to understand the different susceptibilities of these species to polynuclear hydrocarbon-induced mammary tumorigenesis. The effect of pretreatment with several known mixed function oxidase inducers on these activities was studied in both species. Control hamster hepatic benzo(a)pyrene-hydroxylase (BPH) activity was considerably greater than that of the rat. Aroclor was the only inducer to significantly increase hamster hepatic BPH activity, and this by only two-fold. 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene had no effect on hamster liver BPH activity while beta-naphthoflavone (BNF) slightly inhibited this activity. All compounds examined were potent inducers of hepatic BPH and cytochrome P450 in the rat. Control hamster mammary microsomal BPH activity was much lower than the hepatic level, but was fourfold greater than the corresponding level for the rat. All the pretreatments caused similar increases in mammary activity in both species, BNF being the most effective. The ability of control hamster hepatic microsomes to metabolize BP was considerably greater than for the rat. The results indicated that rat and hamster mammary gland microsomes, as well as those of liver, are capable of metabolizing BP. All the pretreatments investigated induced mammary activity in both species, but the rat activity was more inducible than that of the hamster. It was therefore suggested that metabolic activation of carcinogenic polycyclic hydrocarbons can occur in the mammary gland itself. (16 Refs)

16. RELATIONSHIP OF METABOLIC ACTIVATION OF N-HYDROXY-N-ACYLARYLAMINES TO BIOLOGICAL RESPONSE IN THE LIVER AND MAMMARY GLAND OF THE FEMALE CD RAT.

Shirai T, Fysh JM, Lee M, Vaught JB, King CM
(c/o King) Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4346-4353 1981

Ip injection of the N-formyl, N-acetyl, or N-propionyl derivatives of N-hydroxy-4-aminobiphenyl, N-hydroxy-2-acetylaminofluorene, or N-(4-biphenyl)glycolamide disclosed that the ability of these compounds to induce mammary tumors in the female CD rat was greater if the compound was able to be metabolized to a reactive product by one of two soluble enzymes obtained from both the liver and mammary gland. A similar but weaker association between the formation of gamma-glutamyltranspeptidase-positive foci and cellular altered foci of the liver was also observed. The enzyme related to the tumorigenicity of these compounds was characterized by a highly specific capacity to form adducts from the acetyl and propionyl derivatives. The other enzyme exhibited greater activity with N-formyl substrates. The two enzyme activities were separable by ion-exchange chromatography on DEAE-cellulose and by gel filtration of Sephacryl. Liver microsomes also possessed the capacity to activate both the formyl and acetyl derivatives to reactive species; formyl substrates were 7 to 8x more active than acetylated compounds. The microsomal activities and the formyl-preferring soluble enzyme were inhibited by diethyl-p-nitrophenylphosphate, a microsomal deacylase inhibitor. The cytosolic enzymes that are most active with the acetyl and propionyl substrates were little affected by this organophosphate compound. The microsomal activation was not due solely to deacylation of the hydroxamic acids, since formylated and acetylated substrates were hydrolyzed at approx the same rates. (Author abstract) (37 Refs)

17. STUDIES IN THE METABOLISM OF CARCINOGENIC POLYCYCLIC HETEROAROMATIC COMPOUNDS. I. THE HEPATIC MICROSOMAL METABOLISM OF 7-METHYLBENZ[C]ACRIDINE.

Ireland CM, Holder GM, Ryan AJ
(c/o Holder) Dept. Pharmacy, Univ. Sydney, New South Wales 2006, Australia
Biochem Pharmacol; 30(19):2685-2690 1981

An enzyme assay for the metabolism of the carcinogenic aza-aromatic polycyclic compound 7-methylbenz[c]acridine has been developed using a modification of a radiochemical assay described for the polycyclic aromatic hydrocarbon benzo[a]pyrene by DePierre et al and Van Cantfort et al. When the activities of controlled microsomes and microsomes of phenobarbital-, 3-methylcholanthrene- and 7-methylbenz[c]acridine-pretreated animals were compared, strong similarities were displayed toward oxidation of benzo[a]pyrene and 7-methylbenz[c]acridine. These similarities were seen in turnover numbers, Michaelis constants, and inducibility of both enzyme systems. 7-Methylbenz[c]acridine afforded a Type I difference spectrum with 3-methylcholanthrene-pretreated microsomes. It is suggested that 7-

methylbenz[c]acridine is oxidized by the same or a similar set of enzymes which is responsible for benzo[a]pyrene metabolism. (Author abstract) (39 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

18. PRESENCE OF ANTI-GAMMA-FA-REACTIVE ANTIGENS IN SPONTANEOUS AND CARCINOGEN-INDUCED MALIGNANCIES OF EXPERIMENTAL ANIMALS.

Higgins PJ, Tong C, Borenfreund E

Lab. Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Oncology; 38(6):340-345 1981

Immunochemical analysis of various tumors, representing 12 different tissue sites of origin, revealed a gamma-fetal antigen(gamma-FA)-like component in 17 of 23 malignant neoplasms of the mouse. This antigen was identified in extracts of spontaneous and carcinogen-induced murine tumors as well as in extracts of hepatic tumors initiated in the rat with diethylnitrosamine. The occurrence of gamma-FA in 75% of the malignant tumors examined and its presence in the sera of rodents bearing transplanted and primary cancers suggests an associative relationship of potential diagnostic value. This possibility is supported by the observation that immunoprecipitable gamma-FA appeared in the sera of hepatocarcinogen-treated rats several wk prior to the detection of alpha-fetoprotein. (Author abstract) (26 Refs)

19. HEPATITIS B VIRUS PROFILE OF HEPATOCELLULAR CARCINOMA IN THE PHILIPPINES.

Lingao AL, Domingo EO, Nishioka K

Immunology Section, Dept. Medicine, UP-PGH Medical Center, Taft Ave., Manila, Philippines

Cancer; 48(7):1590-1595 1981

The hepatitis B virus (HBV) profile was investigated in 104 age-grouped hepatocellular carcinoma (HCC) patients and 84 controls from the Philippines. The HCC-control percent positivities of the HBV parameters are: HBsAg: 70-18; anti-HBs: 25-37; anti-HBc: 94-35; HBeAg: 5-2; anti-HBe: 60-30; HBV exposure rate: 97-57, current infection: 80-31. Male HCC anti-HBs positivity is significantly lower than in controls. Female HCC patients' anti-HBs are also lower than controls, but this difference is not statistically significant. Simultaneous presence of HBsAg and anti-HBs was found only in male HCC patients. The mean anti-HBc titer of anti-HBs-positive HCC is higher than that of controls. That of HCC patients negative for both HBsAg and anti-HBs is also higher than the corresponding controls. Anti-HBe positivities of infected and noninfected but previously exposed HCC patients are not significantly different, in contrast to noninfected previously exposed controls whose anti-HBe is lower than those with current infection. The exposure rate prevalence of current infection, and the antibody responses to HBV of HCC patients suggest a close relationship between the two conditions in the Philippines. (Author abstract) (36 Refs)

20. DISCRIMINANT ANALYSIS OF THE FACTORS CAUSING HEPATOMA IN YAMANASHI PREFECTURE (MEETING ABSTRACT).

Inaba Y

Dept. Hygiene, Juntendo Univ., Sch. Medicine, Bunkyo-ku, Tokyo 113, Japan

Nippon Eiseigaku Zasshi; 36(1):187 1981

The data for 62 hepatoma patients and 62 control patients were selected from the patient-control studies conducted in Yamanashi Prefecture for about 2.5 yr beginning in 1977. Five risk factors, hepatitis B surface (HBs) antigen (X1), history of schistosomiasis japonica (X2), daily intake of alcohol (X3), history of transfusion (X4) and schistosoma skin test (X5) were selected. The absence of a factor was designated as 1 and its presence as 2 on a computer, and the discriminant coefficient of each factor was calculated by using the Statistical Packages for the Social Sciences Program of the Computer Center, University of Tokyo. A significant difference between the hepatoma group and control group was obtained for the scores of the HBs antigen, history of schistosomiasis japonica and daily intake of alcohol. The schistosoma skin test alone showed a negative correlation, and this may not be unrelated to the immunopotential of the hepatoma group. The discriminant score for the hepatoma and control groups were obtained and the cumulative percentages were calculated. If the positive discriminant score was assigned to the hepatoma group and negative discriminant score to the control group, the predicted results agreed with the actual results in 99 out of 124 patients. There were 19 false-negative entries and 6 false-positive entries. The discriminant formula $Y = 1.80X1 + 1.67X2 + 1.04X3 + 1.00X4-0.74X5-6.00$ was considered to be effective for predicting hepatoma. (no Refs) (In JPN)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

21. THE SIGNIFICANCE OF HYPERPLASTIC LIVER NODULES AS PRECANCEROUS LESIONS ANALYZED FROM THE VIEWPOINT OF CELL GROWTH.

Okita K, Noda K, Numa Y, Ando K, Miyazaki M, Tsubota W, Sasaki M, Matsuda S, Morimoto T, Watanabe S, Fukumoto Y, Kodama T, Takemoto T, Nagamine Y

First Dept. Internal Medicine, Yamaguchi Univ., Sch. Medicine, Ube-shi, Yamaguchi Prefecture 755, Japan

Kanzo; 22(4):559-564 1981

The phenotypic similarities of hyperplastic liver nodules and hepatomas are well recognized. However, there are two kinds of hyperplastic nodules, one with reversible and one with irreversible character, which may be closely linked to the induction of hepatoma. Therefore, we tried to analyze these characters in regard to cell growth. We concluded that it might be difficult to determine the reversibility or irreversibility of the nodules from the incidence of DNA-synthesizing cells, although of course it is possible that the nodules with a low incidence of S-phase cells could be nongrowing. On the other hand, a study of ploidy by means of cytophotometry showed that huge nodules over 10 mm in diameter could be 'quiet' nodules not related to carcinogenesis. (21 Refs) (In JPN)

22. HISTOCHEMICAL CHANGES IN ATPASE DISTRIBUTION DURING HEXACHLOROCYCLOHEXANE INDUCED HEPATOCARCINOGENESIS IN INBRED SWISS MICE.

Bhatt DK, Nigam SK, Aravinda Babu K, Lakkad BC, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(7):621-624 1981

The distribution of ATPase at gross and cellular levels during hepatocarcinogenesis induced by technical grade hexachlorocyclohexane (BHC) in male inbred Swiss mice was investigated. The animals received 500 ppm BHC in diet for 2, 4, and 6 mo. After 2 mo, the periportal areas in the liver were intensely stained in the animals fed BHC compared to central vein areas. In control preparations, hepatocytes in central and periportal areas were homogeneously stained. Hepatocytes in the BHC animals in the central vein area showed strong activity on the bile canaliculi and plasma membranes. After 4 mo exposure to BHC, neoplastic nodules showed marked decrease in ATPase activity. The plasma membrane and bile canaliculi had diminished ATPase activity. After 6 mo exposure, the liver tumors which had developed showed intense ATPase activity in the plasma membrane of tumor cells and considerably diminished or absent activity on the nucleus. (24 Refs)

23. DISTRIBUTION OF CYCLIC 3',5'-PHOSPHODIESTERASE, MONOAMINE OXIDASE AND BETA-GLUCURONIDASE IN LIVER TUMOURS INDUCED BY TECHNICAL GRADE HEXACHLOROCYCLOHEXANE IN INBRED SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Aravinda Babu K, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(7):625-629 1981

Male inbred Swiss mice were fed 500 ppm technical grade hexachlorocyclohexane (BHC) in their diet for 8 mo after which time the distribution of cyclic 3',5'-phosphodiesterase (cPDE), monoamine oxidase (MAO), and beta-glucuronidase (bGLU) was investigated. There was no difference in mortality between the experimental and control groups. All treated animals developed hepatocellular carcinomas. The distribution of cPDE in the tumor increased, particularly in large droplet-like cytoplasmic activity. In control animals, the MAO activity in the liver was homogeneous in all areas. MAO activity in the tumor was mainly cytoplasmic and nuclei remained unstained. bGLU activity decreased considerably in tumors and nontumor parts of treated animals compared to controls. bGLU activity was very strong in vacuoles. (24 Refs)

24. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

This review deals with premalignant liver lesions in rats fed N-2-acetylaminofluorene (AAF) or diethylnitrosamine (DEN), DNA alterations in premalignant lesions, and cellular responses to skin tumor promotors such as tetradecanoylphorbol acetate (TPA). Rats fed four cycles of AAF exhibited persistent hepatic nodules having increased mitotic activity and altered DNA. Similarly, premalignant lesions induced by DEN and phenobarbital showed an increase in altered DNA, which paralleled the increase in risk of hepatoma. The broad effects of tumor promotion consist of the induction of proliferation of an initiated cell population and the appearance of aggregates of altered cells. Tumor promotors such as TPA heighten the mitotic responses in these cells and eventually induce epigenetic programmatic alterations. (38 Refs)

25. ULTRASTRUCTURE OF HEPATIC ANGIOSARCOMA IN RATS INDUCED BY VINYL CHLORIDE.

Spit BJ, Feron VJ, Hendriksen CF

Institute CIVO-Toxicology and Nutrition TNO, P.O. Box 360, 3700 AJ Zeist, The Netherlands

Exp Mol Pathol; 35(2):277-284 1981

The hepatic angiosarcoma studied was from a male Wistar rat having been exposed to vinyl chloride monomer (VCM) by the oral route for 120 wk. Widened sinusoids lined by large electron-lucent, spindle-shaped tumor cells and membrane-bound nuclear-free structures were seen in the transitional zone between the tumor mass and the adjacent liver tissue. In areas merely consisting of tumor tissue the tumor cells had a more angular or irregular shape. The origin of the tumor cells is discussed in light of the characteristic differences between endothelial cells and Kupffer cells described in the literature. Although an endothelial origin of the tumor cells could not be established unequivocally, it was concluded that at present there is little reason to doubt such an origin. (Author abstract) (21 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

26. DNA-DEPENDENT RNA POLYMERASE I FROM HEPATOMAS: COMPARISON OF ACTIVITY LEVELS AND PROPERTIES.

Cavanaugh AH, Thompson EA

(c/o Thompson) Dept. Biology, Univ. South Carolina, Columbia, SC, 29208

Cancer Biochem Biophys; 5(2):125-133 1981

Activity levels of DNA-dependent RNA polymerase I (Pol I; ribonucleoside triphosphate: RNA ribonucleotidyl transferase, EC 2.7.7.6, eucaryotic Type I) have been compared in five transplantable murine hepatomas and livers of three inbred mouse host strains. Three tumors (H6, H4 and H134) contained about 350-450 units of Pol I activity/g of tissue. Two hepatomas (H129 and BW7756) contained about 120-150 units of activity/g of tissue. Livers contained about 100-150 units/g of tissue. Chromatographic comparisons revealed that hepatoma Pol I is slightly less anionic than the liver enzyme. Thermal denaturation studies were carried out using Pol I partially purified from a high-activity line hepatoma (H6), a low-activity line hepatoma (H129) and livers of the appropriate host strains. Pol I from H6 tumors was denatured at 40 C with a half-time of 2 min. The enzyme from H129 tumors and host livers was denaturated with a half-time of 7 min. These data indicate that hepatoma H6 expressed a structural variant of Pol I. This is the first Pol I variant ever reported. (Author abstract) (21 Refs)

27. POLYAMINE CONCENTRATION, ACTIVITY OF THE RIBOSOMAL DISSOCIATION FACTOR AND PROPORTION OF RIBOSOMES ACTIVE IN PROTEIN SYNTHESIS IN THE 4-DIMETHYLAMINOAZOBENZENE-INDUCED RAT HEPATOMA.

Comolli R, Riboni L
Centro per lo Studio della Patologia cellulare del C.N.R., Universita di Milano, via Mangiagalli, 31, I-20133 Milano, Italy
Cancer Lett; 14(1):77-83 1981

The activity of the ribosomal dissociation factor in the high salt ribosomal wash and in the particle free cytoplasm of 4-dimethylaminoazobenzene (DAB)-induced liver tumors as compared to the livers of control rats was investigated and the proportion of ribosomes active in protein synthesis and the concentration of the polyamines spermine, spermidine and putrescine were determined. While the spontaneous dissociation of ribosomal preparations from DAB hepatoma was higher than from control liver, the addition of ribosomal wash extract and supernatant extract from the hepatoma caused a decrease in dissociation. The addition of control liver dissociation factor extracts to normal ribosomal preparations caused an increase in dissociation into active subunits. The proportion of ribosomes active in protein synthesis as indicated by sucrose density gradient analysis was significantly lower in tumor tissue. A significant decrease of putrescine in the DAB tumor cell extracts was noted, compared to normal rat liver. The spermidine/putrescine and (spermidine plus spermine)/putrescine ratios increased, predisposing towards association of the subunits. (22 Refs)

28. DOSE-DEPENDENCY OF 2-ACETYLAMINOFLUORENE BINDING TO LIVER DNA AND HEMOGLOBIN IN MICE AND RATS.

Pereira MA, Lin LH, Chang LW
Health Effects Res. Lab., US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicol Appl Pharmacol; 60(3):472-478 1981

Binding of 2-acetylaminofluorene (2-AAF) to liver DNA and Hb in Sprague-Dawley rats and CD-1 mice of both sexes was determined to test proposals that Hb binding correlates with target organ DNA binding and carcinogenicity. In both species, 2-AAF binding to liver DNA and HB increased as a linear function of dose (1-100 umoles/kg, po). This indicated that the formation of reactive 2-AAF liver metabolites also was linearly related to dose. No sex difference was observed in 2-AAF macromolecular binding, except for an apparent higher liver DNA binding in female mice than in male mice. DNA binding was only 7x greater and Hb binding only 2.5x greater in rats than mice; thus the binding did not reflect the 246x greater carcinogenicity of 2-AAF in rat liver. The results indicated that Hb binding can be used to predict DNA binding and the systemic dose; however, the extent of DNA binding does not predict carcinogenic potency. (20 Refs)

29. FEEDBACK CONTROL OF CHOLESTEROL BIOSYNTHESIS IN RATS FED THE LIVER CARCINOGENS BENZIDINE AND 2-ACETYLAMINOFLUORENE.

Depass LR, Morris MD
Bushy Run Res. Center, R.D. 4, Mellon Road, Export, PA, 15632
Cancer Biochem Biophys; 5(2):91-95 1981

Dietary feedback control (DFC) of hepatic cholesterol synthesis is absent in hepatomas of trout, mouse, rat and man. DFC has also been shown to be defective in rats fed several liver carcinogens, including 2-acetylaminofluorene (AAF). These studies have led to the hypothesis that loss of normal DFC is an early and necessary event in the development of liver cancer. To test this hypothesis, we fed the liver carcinogens benzidine (0.006% in drinking water) or AAF (0.05% in chow) to male Sprague-Dawley rats for either 3 or 6 wk. We measured cholesterol synthesis as the incorporation of 2-14C-acetate into digitonin-precipitable sterols by liver slices. DFC was tested by adding 2% cholesterol to the diet for 3 days prior to sacrifice. DFC was defective in the AAF-fed rats but was normal in the benzidine-treated rats. These results are at variance with the previously stated hypothesis and, for the first time, suggest that defective DFC is not a consistent finding in the early stages of liver carcinogenesis. Additional research is necessary to explain why DFC is altered by exposure to some liver carcinogens such as AAF but unaffected by exposure to others such as benzidine. (Author abstract) (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

30. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.

Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981

Recent studies on the carcinogenic effects of phenoxy acids and chlorophenols in occupationally exposed subjects are reviewed. Relationship between exposure to phenoxy acids and chlorophenols and malignant mesenchymal soft-tissue tumors was found in two case-control studies in Sweden. Increased risk of malignant lymphoma was also demonstrated in another study. Malignant lymphoma, acute leukemia, and malignant mesenchymal soft-tissue tumors were found at significantly increased incidence among workers exposed to (2,4,5-trichlorophenoxy)acetic acid 2,4,5-trichlorophenol, and the impurity 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). TCDD was found to induce malignant mesenchymal soft-tissue tumors, and 2,4,6-trichlorophenol caused increased incidence of hepatocellular carcinoma, malignant lymphoma, and leukemia in rats. (15 Refs) (In SWE)

31. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.

Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

A set of maps which display the patterns of cancer mortality in China has been prepared and published by the China Map Press. The 200 page atlas was edited by the National Cancer Control Office of the Ministry of Health and the Nanjing Institute of Geography of the Chinese Academy of Sciences on the basis of a nation-wide cancer mortality survey. The Cancer Institute of the Chinese Academy of Medical Sciences with related Colleges, Universities and Institutes provided the data and took part in the preparation of the atlas, which is published both in Chinese and English. Fifty eight maps and several dozen charts depict, in seven colors, the mortality distribution in the 2,392 counties and county-level administrative units of nine types of cancer common in China - stomach, esophagus, liver, cervix, lung, colon and rectum, breast, nasopharynx, and leukemia as well as five less common cancers - brain tumors, malignant lymphoma, cancer of the bladder, of the penis, and choriocarcinoma. The Atlas of Cancer Mortality will be an important new aid for cancer control and research in the People's Republic of China. (Author abstract) (10 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
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2. THE CARCINOGENICITY OF ARSENIC.
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Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
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4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
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5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

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Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
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Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
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8. BENZENE AS A RISK FACTOR.
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9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
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J Am Dent Assoc; 103(3):429-434 1981

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13. NUTRITIONAL MODULATION OF CANCER.
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Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
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14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.
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17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
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(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

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19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
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Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
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Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
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Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

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Zakour RA, Kunkel TA, Loeb LA
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26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
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Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
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27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
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Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
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MARCH, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. ADVANCES IN CANCER EPIDEMIOLOGY IN SOUTH AFRICA.

Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
S Afr Cancer Bull; 25(1/2):9-18 1981

The epidemiology of cancer in South Africa (SA) is discussed through the review of four papers on the cancer pattern in black gold miners in SA (1964-79), comparison of cancer mortality rates in SA with those of other countries, cancer mortality rates for blacks, whites, coloreds, and Asians in SA (1970-77), and the cancer problem among blacks in SA. Mortality rates were compared for all groups (SA and US: United States). Much less cancer was found in the SA urban black than in any of the other groups. The SA colored community had rates which were very nearly the highest for most of the common cancers for each site of almost all the cancers considered. The cancer pattern in SA whites of both sexes was similar to that of US whites. Whereas US blacks had consistently higher rates than US whites but the same pattern, SA blacks had a different cancer pattern to that of either the coloreds or whites in SA. The pattern for SA blacks comprised high rates for esophagus, liver, and lung cancer in males, and for cervix and esophagus cancer in females, while rates for colorectum, stomach, and female breast cancer were low. Colored males had the highest cancer risk in SA. The colored female is not nearly as much at risk as the male. Comparison between SA colored and US black males showed cancer rates to be higher in the coloreds. The overall mortality rate for cancer in SA urban blacks was lower than that for SA whites or coloreds, both males and females. The implications of these studies are discussed. (17 Refs)

2. NATIONAL SURVEY OF CANCER MORTALITY IN CHINA (MEETING ABSTRACT).

Ha HW, Li B, Li J
No affiliation given
First UICC Conference on Cancer Prevention in Developing Countries, August 25-29, 1981, Nagoya, Japan. International Union Against Cancer 368 pp., 1981.

A nation-wide retrospective survey of cancer mortality for a 3 yr period was conducted in China. Three hundred and ninty-five cities and 2,136 counties were covered with a population of more than 850 million. Data were collected on mortality due to 56 causes, including 15 types of cancers. They were repeatedly checked were considered reliable. Cancer was found to be the second and third leading causes of death among males and females. It was the first cause of death among 429 counties in the male, and among 161 counties in the female. Approx 700,000 people would die of cancer each yr in China with a crude mortality rate of 73.99 per 100,000. There were 13 provinces in China in which cancer motality rate (age adjusted to the world standard population) exceeded 100 per 100,000. In sequence of anatomic site, cancers of the upper alimentary tract were the most common. Stomach cancer occupied the first place while esophageal cancer ranked second and liver cancer was third in frequency. These three cancers accounted for 60% of all cancer deaths. In sequence among the national minorities, cancer rates were highest among the Kazak, the Hui and the Korean. The Miao and Yi tribes gave the lowest rates. Some cancers were common throughout China while others differed remarkably among the various geographical regions. These geographical distributi on characteristics are to be reported in the Atlas of Cancer Mortality of the People's Republic of China. (no Refs)

3. A STUDY OF THE GEOGRAPHICAL PATTERN OF CANCER MORTALITY FOR SELECTED SITES BY MEANS OF FACTOR ANALYSIS.

Inaba Y, Yanai H, Takagi H, Yamamoto SI
Dept. Hygiene, Juntendo Univ., Japan
Soc Sci Med [Med Geogr]; 15(1):233-244 1981

Factor analysis of the geographical distribution of cancer mortality in 46 Japanese prefectures during 1958-1971 revealed a significant correlation between the rate of primary industry and skin, prostate, lymphoid tissue, or bladder cancer and leukemia in men. In women, uterine and liver cancer and leukemia correlated positively with natural environmental factors (temperature, precipitation). Lung, intestinal, and oral cancer correlated with population density and appeared to be related to industrialization or urbanization. There was also a significant positive correlation between the rate of primary industry and pancreas and bile duct cancer in women. Esophageal cancer did not correlate with the primary industry rate, the natural environmental factors, or population density. Food consumption in Japan and 24 other countries also was analyzed. Despite the different data sources, similar clustering of cancer sites was noted; ie, prostate, skin, and leukemia for men, skin and leukemia for women, and intestines and lungs for both sexes. (15 Refs)

4. HUMAN LIVER TUMORS IN RELATION TO STEROIDAL USAGE (MEETING ABSTRACT).

Barrows GH, Christopherson WM
University of Louisville School of Medicine, Louisville, KY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Since 1973, a number of investigators have reported an association between liver neoplasia and steroid usage. Through referral material the authors have examined the histology of over 250 cases of hepatic neoplasia, most in patients receiving steroid medications. The majority have been benign, predominantly focal nodular hyperplasia (55%) and the hepatocellular adenoma (39%). The av age was 31.4 yr. Eighty-three precent had significant steroid exposure with an av duration of 71 mo for focal nodular hyperplasia and 79.6 mo for hepatocellular adenoma. The type of estrogenic agent was predominantly mestranol. A distinct clinical entity of life threatening hemorrhage from the lesion occurred in 31% of patients with hepatocellular adenoma and 9% of patients with focal nodular hyperplasia. Recurrence of benign tumors has occurred in some patients who continued using steroids and regression has been observed in patients who had incomplete tumor removal but discontinued steroid medication. Medial and intimal vascular changes have been present in a large number of the benign tumors. The relationship of these vascular changes to oncogenesis is unclear, but similar lesions have been described in the peripheral vasculature associated with steroid administration. A number of hepatocellular carcinomas have also been seen. Of significance is the young age of these patients and lack of abnormal histology in adjacent non-neoplastic liver. A striking number of the malignant hepatocellular tumors have been of the uncommon type described as 'eosinophillic hepatocellular carcinoma with lamellar fibrosis'. The epidemiology of liver lesions within this series is difficult to assess since the material has been referred from very diverse locations. (no Refs)

5. CANCER RISKS OF MEDICAL TREATMENT. PART II: POTENTIALLY CARCINOGENIC MEDICATIONS IN CURRENT USE.

Schottenfeld D
Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY
Clin Bull; 11(2):75-82 1981

Experimental and epidemiological data on the carcinogenicity of currently available drugs are reviewed. Patients treated with cytotoxic antineoplastic agents are at increased risk for bladder cancer and acute nonlymphocytic leukemia. Immunosuppressive agents are associated with development of lymphoreticular malignancies in renal transplant recipients. Estrogen administration increases the risk of endometrial and breast carcinoma in menopausal and postmenopausal women. Oral contraceptives have been shown to be associated with endometrial cancer, uterine cervical dysplasia, and cervical carcinoma in situ. Oral contraceptives reduce the risk of benign breast diseases. Androgenic anabolic steroids have been found to cause liver carcinoma. Methoxypsoralen in the presence of UV increases the risk of skin carcinoma. Phenacetin-containing analgesics have been shown to cause chronic interstitial nephritis, carcinoma of the renal pelvis, and bladder carcinoma. Potentially carcinogenic but cost-effective drugs should be prescribed at the lowest dose and for the shortest period of time. (59 Refs)

6. THE LIVER AND 'THE PILL'. PART 2: HEPATIC TUMORS.

Eisenburg J
Med. Univ.-Klinik II, Klinikum Grosshadern, Marchioninistrasse 15, 8000 Munchen 70, W. Germany
Fortschr Med; 99(38):1527-1532 1981

The relationship between the use of oral contraceptives and the development of benign or malignant tumors of the liver is discussed. Types of benign hepatic tumors are listed, and features of hepatocellular adenoma and focal nodular hyperplasia and described in detail. Hepatocellular carcinoma is examined with regard to the mechanism of its development, diagnosis, clinical features, prognosis, and treatment. Selected features of the relationship between use of oral contraceptives and occurrence of liver tumors are illustrated through a summary of the case histories of eight patients (22-45 yr old). All of the patie nts used oral contraceptives for 5 to 14 yr, and all subsequently developed benign liver tumors. Three of the patients were asymptomatic at the time of diagnosis. The final diagnosis was made through laparoscopy in four patients and through laparotomy in four. In one patient, a hepatoma developed in an area of benign focal nodular hyperplasia within 2 yr of the original diagnosis. It is suggested that women who used oral contraceptives for long periods should be screened for hepatic changes at regular intervals. (6 Refs) (In GER)

7. OTHER IATROGENIC CANCERS (MEETING ABSTRACT).

Ross RK
No affiliation given
The Causes of Cancer, November 6, 1981, Los Angeles, California California Hospital Medical Center; 1981

The majority of iatrogenic cancers fit into two categories: those induced by diagnostic or therapeutic radiation and those induced by prescription drugs. Since radiation induced cancer has already been discussed in detail, this session will be primarily concerned with drugs as causes of human cancer. Several drugs which are now recognized as causes of human cancer have been detected only because of the rarity of the cancer in the absence of the drug. For example, the association between a mother's use of diethylstilbestrol during pregnancy and the development of clear cell adenocarcinomas of the vagina in her daughter decades later was only detected because several cases of this extremely rare tumor were noted in a single hospital in a rather short period of time. Similarly, in a case-control study at University of Southern California, it was demonstrated that risk to women or a rare form of liver cancer, benign liver adenoma, was strongly related to duration of use of oral contraceptives. It seems likely that such relationships exist for more common cancers by go undetected either because no one suspects this relationship or the relationship is difficult to study in the face of other factors causing the same disease. In fact, several such relationships with more common cancer sites have been demonstrated in recent yr. Use of amphetamines has been shown to increase one's risk to Hodgkin's disease some 4-6 fold, use of immunosuppressive drugs has been demonstrated to greatly increase risk to non-Hodkins' lymphomas and use of estrogen replacement therapy, perhaps the most widely studied group of drugs in terms of cancer risk, increases risk of endometrial cancer and breast cancer. (no Refs)

8. MORTALITY AND INDUSTRIAL HYGIENE STUDY OF WORKERS EXPOSED TO STYRENE (MEETING ABSTRACT).

Beaumont JJ, Meinhardt TJ, Okun AH, Crandall MS
National Institute for Occupational Safety and Health, Cincinnati, Ohio
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Recent research indicates that workers exposed to styrene may experience chronic health problems: 1) Studies have shown an increase of deaths due to leukemia among styrene-butadiene rubber workers; 2) Styrene has been shown to be mutagenic after liver microsomal activation; 3) Styrene oxide, a metabolite of styrene, has been shown to be mutagenic by the Ames test. Hepatotoxicity and carcinogenicity have been attributed to chronic exposure to styrene metabolites based on animal experiments. To further evaluate the effects of styrene exposure on humans, a retrospective cohort mortality and industrial hygiene study is being conducted. Employees from two boat manufacturing companies in Washington State were selected for study. Styrene exposure started at both facilities in 1957 and a total of 5,359 employees had worked at these plants by the time of the data collection. The personnel records for both companies were microfilmed in October of 1978, and industrial hygiene surveys were conducted during June and August of that yr. The vital status is being ascertained for each worker and death certificates are being sought for those individuals found to be deceased. To verify the completeness of the cohort, the names of all cohort members were matched against the Internal Revenue Service quarterly earnings reports. The cohort will be analyzed by a modified life table where expected numbers of deaths will be calculated based upon United States death rates, adjusted for race, sex, age, and calendar time. Various exposure groups, based upon the industrial hygiene surveys, will also be analyzed separately. (no Refs)

9. PROPORTIONATE MORTALITY STUDY OF FUR DYERS (MEETING ABSTRACT).

Haring MK, Waxweiler RJ, Walrath J
National Institute for Occupational Safety and Health, Cincinnati, OH
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

In recent studies, numerous constituents of oxidative hair dyes were shown to be mutagenic by the Ames test; some were also proven to be carcinogenic, inducing tumors of the liver, lymphatic system or other sites, in laboratory animals. Epidemiologic studies have associated exposure to hair dyes with increased risks of breast, cervical and lung cancers and chromosomal damage among hairdressers and consumers. During the past century, fur dyers have used oxidative dyes extensively to tint and color animal fur. To investigate the health effects of long term exposures to oxidative dyes, a retrospective cohort mortality study is being conducted on 980 fur dyers and processors of the Fur, Leather and Machinists Workers Union who were pensioned between 1952 and 1977. The standardized mortality ratio (SMR), using age-sex-rac e, calendar time, and cause-specific mortality rates for United States, will be calculated for all causes of death including all malignant neoplasms. In addition to oxidative dyes, other possible occupational exposures are saw dust, used to absorb excess dye from furs, and formaldehyde. Analyses of job classifications and ethnic origins also will be conducted. (no Refs)

TUMOR INDUCTION IN ANIMALS

10. CARCINOGEN BIOASSAYS OF SEVERAL PHTHALIC ACID DERIVATIVES AND RELATED COMPOUNDS (MEETING ABSTRACT).

Hartwell WV, Douglas JF
National Toxicology Program, National Cancer Institute, Bethesda, MD, 20205
Toxicologist; 1(1):130 1981

Carcinogenesis bioassays have been conducted with select phthalic acid derivatives and di(2-ethylhexyl)adipate. Test animals were F344 rats and B6C3F1 mice. Only those esters containing the 2-ethylhexanol moiety were considerable carcinogenic. Hepatocellular carcinomas occurred in a dose related fashion in high- and low-dose male and female rats and mice which received diets containing the di-(2-ethylhexyl)phthalate. Di(2-ethylhexyl)adipate was not carcinogenic in rats; however, increased incidences of liver tumors were detected in both male and female mice. In separate studies, increased tumor incidences were not detected in male or female Wistar or Sherman rats fed diets containing di(2-ethylhexyl)phthalate for 104 wk. (no Refs)

11. EXPERIMENTAL LESIONS INDUCED IN RATS BY POLYVINYL CHLORIDE (PVC) COMBUSTION FUMES.

Dessy E, Faa G, Calatri S, Bucarelli A
II Cattedra di Anatomia e Istologia Patologica, Universita di Cagliari, Cagliari, Italy
Boll Soc Ital Biol Sper; 57(11):1278-1281 1981

The effect of pure polyvinyl chloride (PVC) powder combustion fumes was studied in 14 adult white Wistar rats. Forced inhalation of wood combustion fumes was given to eight control rats. The forced inhalation was administered for 1 hr every day during 30-180 days. The rats were sacrificed approx 1 yr after the end of the experiment. While they were exposed to fumes animals were irritable, aggressive, dehydrated, and lost wt. Most significant histological findings were in lung (metaplasia of bronchial epithelium), and liver (enlargement of sinusoidal bed, and activation of Kupffer cells). Animals treated for an extended period of time had marked alopecia of the neck and back, and histologically sebaceous gland hyperplasia. Two rats had three sc tumors, histologically diagnosed as adenocarcinomas (neck, and mammary sites). (7 Refs) (In ITA)

12. CARCINOGENICITY OF INHALED 1,2-DIBROMOETHANE IN RATS TREATED WITH DISULFIRAM (MEETING ABSTRACT).

Wong LC, Winston JM, Hong CB
Midwest Research Institute, Kansas City, MO
Toxicologist; 1(1):130 1981

A chronic inhalation study of ethylene dibromide (EDB) was conducted in Sprague Dawley rats. The study consisted of four groups of rats receiving control air and control diet, 20 ppm of EDB and control diet, control air and 0.05% of disulfiram (DS) in the diet, and 20 ppm of EDB and 0.05% of DS in the diet, over a period of 18 mo. Rats receiving 20 ppm of EDB showed high mortality and an increase in tumor incidences in mammary glands, spleen, adrenals, liver, kidneys, and sc tissues. A combination of 20 ppm of EDB and 0.05% DS in the diet caused earlier deaths and high mortality rate, decreases in body wt gain, food consumption, Hb, hematocrit and RBC counts in rats. This combination of EDB and DS treatment also caused early development and high incidences of tumors in liver, spleen, kidneys, adrenals, thyroids, lungs, mesentary and mammary tumors. In addition, 90% of male rats that received a combination of EDB and DS treatment had testicular atrophy. Addition of DS treatment caused early deaths and high mortality rate, and promoted not only the tumor incidences in various organs and tissues in both male and female rats, but also the testicular atrophy in rats. (no Refs)

13. THE RESPONSE OF THREE INBRED STRAINS OF RAT TO THE CARCINOGEN 1,2-DIMETHYLHYDRAZINE.

Teague CA, Gavin JB, Herdson PB
(c/o Gavin) Dept. Pathology, Univ. Auckland, Private Bag, Auckland, New Zealand
Pathology; 13(3):473-485 1981

Rats of three inbred strains (DA, HS and AS2) were dosed with 1,2-dimethylhydrazine 2HCl (DMH) or saline by gavage weekly for 10 wk. DA and HS rats showed little overt toxic reaction but all AS2 rats died following DMH doses of 30 mg/kg. However, at 10 mg/kg 60% of AS2 rats survived the 30 wk experiment. All DA rats developed a high yield of adenocarcinoma of the bowel (means: males 6.8 tumors/large bowel and 0.8/small bowel; females 2.8/large and 0.08/small bowel) and one-third of the males developed tumors of the ear canal. A smaller proportion (52%) of HS rats developed tumors, specifically bowel tumors (means: male 1.4/large and 0.2/small bowel; females 0.4/large and 0.1/small bowel). Even on the lower dose of DMH AS2 rats showed extensive liver changes including cystic cholangioma (58%), angiosarcoma (25%) and hepatocellular carcinoma (8%) and 83% developed bowel tumors (means: males 2.3/large and 1.5/small bowel; females 3.5/large and 1.0/small bowel). The rapid induction and high yield of bowel tumors, the different toxicity of DMH in AS2 rats, and the differences in relative tumor density both between sexes and in the various segments of the bowel indicate the potential of these strains for studies of carcinogenesis in the bowel. (Author abstract) (32 Refs)

14. LIFE-SHORTENING AND CARCINOGENESIS IN MICE IRRADIATED NEONATALLY WITH X-RAYS.

Sasaki S, Kasuga T
Div. Radiation Hazards, Natl. Inst. Radiological Sciences, Chiba 260, Japan
Radiat Res; 88(2):313-325 1981

Modulation of tumor spectrum and dose-dependent relationship for carcinogenesis after x-irradiation of neonatal B6WF1 mice (200, 400, or 600 R within 24 hr of birth) was investigated. Conditions for radiation were 200 kilovolts peak, with a filter of 0.5 mm Cu plus 0.5 mm Al, half-value layer of 1.2 mm Cu, and a dose rate of 55-60 R/min. Preweaning death rates in mice irradiated with 200 or 400 R were not significantly different from controls. After 600 R 24% died before weaning. Bone marrow of dead mice was markedly aplastic. Mean and distribution pattern of life spans was affected by irradiation. A very high death rate in the early life of x-irradiated mice was attributable to thymic lymphoma. Incidence of neoplastic disease was high in control mice (71% for females and 60% for males). The number of mice bearing one or more primary neoplasms at autopsy increased in x-irradiated groups except for males that received 200 R. The % of mice dying with multiple primary neoplasms increased in females irradiated with 200 or 400 R. Neoplasms which increased after neonatal irradiation included thymic lymphoma and liver, pituitary and ovarian tumors. Neoplasms decreasing in incidence included lymphoreticular tissue tumors except thymic lymphoma, uterine tumor, and lung tumor in the highest dose group. (25 Refs)

15. CHRONIC TOXICITY AND RISK ASSESSMENT IN MICE EXPOSED TO BENZIDINE DIHYDROCHLORIDE (MEETING ABSTRACT).

Littlefield NA, Nelson CJ, Schieferstein G
National Center for Toxicological Research, Jefferson, AR
Toxicologist; 1(1):129 1981

Benzidine, recognized as a bladder carcinogen in man and as a liver carcinogen in experimental animals, is the chemical basis of as many as 200 commercial dyes. It has recently been demonstrated that physiological processes can metabolize these dyes to release benzidine, thereby creating a potential exposure hazard. To assess this hazard, both sexes of F1 hybrid (homogeneous) and F2 (heterogeneous) mice from a BALB/c male and C57BL/6 female cross were exposed for their respective live spans to benzidine dihydrochloride in their drinking water at concentrations of 0, 30, 40, 60, 80, 120, and 160 ppm for males and 20, 30, 40, 60, 80, and 120 ppm for females. Animals were removed from the study only when they were dead or moribund. This study was terminated after 33 mo of exposure. Using the endpoint of hepatocellular adenomas and carcinomas, the Armitage-Doll multistage model was used to describe the tumor rates in the experimental dose range and obtain the upper confidence level on tumor rates. Linear interpolation was used between 0 dose and the upper confidence level of the lowest experimental dosage for predicting potential low dose tumor rates. Dose response effects on body wt, survival, and liver neoplasms were noted in both strains. For each of the endpoints, the females were more susceptible than males and the F1 (homogeneous) strain was more susceptible than the F2 (heterogeneous) strain. The calculated virtually 'safe' dose predicted to produce less than one per million F1 female mice with a liver tumor is 0.04 ppb. One ppb of benzidine dihydrochloride in the drinking water of these mice would theoretically produce liver tumors in less than 2.49 mice per 100,000 population. (no Refs)

16. DOSE RESPONSE STUDIES OF CARCINOGENESIS IN RATS BY NITROSODIETHYLAMINE.

Lijinsky W, Reuber MD, Riggs CW
Chemical Carcinogenesis Program and Information Systems Dept., Frederic Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(12):4997-5003 1981

A dose-response study was conducted in Fischer rats with nitrosodiethylamine, which was administered in regulated amounts as a soln in drinking water. Groups of 20 female rats each received a different treatment; one group consisted of 12 animals; one of the groups was untreated. The concentrations of the soln fed ranged from 113 to 0.45 mg/liter at six successive concentrations differing by a factor of 2.5. The treatment times were 17 wk at the highest concentration; 22 wk with 45 mg/liter; and 30 wk with 18, 7, 2.8, 1.1 and 0.45 mg/liter. The two lowest dose levels were also given for 60 wk, and the 0.45-mg/liter dose levels were also given for 104 wk. Animals were allowed to die naturally with tumors, and the time to death with tumors was an index of the potency of treatment. In the top four treatment groups, the potency measured in this way was proportional to the total dose of carcinogen administered. At all other doses, survival time was much less dependent on the dose administered, whether or not tumors were induced by the treatment. The principal tumors found were in the upper gastrointestinal tract, mainly the esophagus, at all doses. In the two highest dose groups, there was a high incidence of liver tumors also. There were few liver tumors in the lower dose groups, but there was a dose-related incidence of tumors of the upper gastrointestinal tract. It was remarkable that a nitrosodiethylamine concentration of 0.45 mg/liter (0.45 ppm) administered for 104 wk induced tumors of the upper gastrointestinal tract in 70% of the treated rats. (Author abstract) (15 Refs)

17. INVASIVENESS OF HYPERPLASTIC NODULE CELLS FROM DIETHYLNITROSAMINE-TREATED RAT LIVER.

Wanson JC, De Ridder L, Mosselmans R
(c/o Ridder) Lab. Experimental Cancerology, Dept. Radiotherapy, Univ. Hosp., De Pintelaan 135, B-900 Gent, Belgium
Cancer Res; 41(12):5162-5175 1981

Administration of diethylnitrosamine po to female Sprague-Dawley rats induces hepatocellular lesions antecedent to hepatocarcinoma (altered foci and hyperplastic nodules). We have tested hepatocytes from hyperplastic nodules for their invasiveness in vitro, which is a marker for mali gnancy. The hyperplastic nodule cells are compared with control liver cells and hepatocarcinoma cells. Control liver tissue and the hepatocarcinoma are collected as fragments taken directly from the rat liver. Nodules, on the other hand, isolated by collagenase perfusion of the liver, are collected on a filter. The fragments of normal liver, the nodules, and the hepatocarcinomas were brought in contact with precultured 9-day-old embryonic chick heart fragments for attachment to each other to form confronting cultures. After attachment, the confronting cultures are incubated at 37 C on a gyratory shaker for 24 hr to 14 days. Hepatocytes from the nodules show progressive invasion into the precultured heart fragments in the same way as the hepatocarcinoma cells after 3 to 14 days in vitro. The control hepatocytes from the liver fragments showed no invasion. We conclude from these observations that the cells of the nodules must be considered as malignant altered hepatocytes, for they show progressive invasiveness in vitro. (Author abstract) (38 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

18. EPIGENETIC MECHANISMS OF LIVER TUMOR PROMOTERS AND IMPLICATIONS FOR HEALTH EFFECTS (MEETING ABSTRACT).

Williams GM
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Cells in vivo and in vitro exchange molecules through specialized membrane organelles known as gap junctions. Intercellular transfer of growth and/or differentiation regulating factors could be involved in suppressing the growth of initiated neoplastic cells. Several liver tumor promoters have been found to inhibit intercellular communication in an in vitro liver culture system. This effect on the cell membrane could thus, be the basis for the tumor promoting activity of these chemicals. Such an epigenetic mechanism would account for the requirement for high doses and prolonged exposure for certain liver tumor promoters. In addition, it implies a distinct type of health risk analysis. A number of chemicals particularly halogenated hydrocarbons, produce primarily or exclusively an increase in liver tumors in rodents which display a spontaneous incidence of such tumors. Several of these chemicals exert an inhibition of intercellular communication and thus, may be functioning as liver tumor promoters. Accordingly, the health risk analysis for these chemicals is different from that for genotoxic carcinogens. (no Refs)

19. TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

Herren SL, Pereira MA
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

An initiation/promotion bioassay using gamma glutamyl transpeptidase (GGTase) positive foci as the endpoint has been developed that can detect the carcinogenic potential of chemical carcinogens. GGTase-positive foci are presumed to be areas of initiated hepatocytes in contrast to the GGTase-positive areas of Zone 1 diffusion observed with compounds such as phenobarbital and saccharin. To evaluate the tumor promoting activity of phenobarbital, rats were administered diethylnitrosamine (DENA), 0.3 mmole/kg, followed by 500 ppm phenobarbital in their drinking water. After six wk of phenobarbital promotion, the rats had an increased incidence of foci as compared to non-phenobarbital treated rats. By 50 wk of phenobarbital promotion, the number of foci in the non-promoted animals equaled the number observed with promotion. This demonstrated that the initiator determined the ultimate number of foci while the promoter decreased the latent period required for the observation of foci. In an experiment to determine the effect of phenobarbital on the stability and progression of GGTase-positive foci, rats received a 2/3 partial hepatectomy, followed 24 hr later by DENA (0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for eight wk. After eight wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number of foci/cm 2 observed in rats continued on phenobarbital treatment leveled off after 10 wk of continuous promotion approached that observed with continuous phenobarbital promotion, while the number of foci/cm2 in the rats taken off phenobarbital initially decreased. However, 56 wk after the administration of DENA, the number of foci/cm2 from the rats removed from phenobarbital promotion approached that observed with continuous phenobarbital promotion, although the size of the foci from the rats on continuous promotion was larger. After 81 wk, all six (100%) of the rats on continuous promotion had liver tumors while only three of six (50%) rats removed from promotion had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the size of DENA initiated foci as well as ultimately increasing the incidence of liver tumors. (no Refs)

20. QUANTITATIVE ASPECTS OF DRUG-MEDIATED TUMOR PROMOTION IN LIVER AND ITS TOXICOLOGICAL IMPLICATIONS (MEETING ABSTRACT).

Kunz HW, Schwarz M, Tennekes HA

The German Cancer Research Centre, Heidelberg, W. Germany

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Chronic exposure of rodents to high dose levels of drugs, food additives and env ironmental chemicals frequently results in liver enlargement. Several of these compounds have been found to enhance the incidence of liver tumors in animals briefly exposed previously to hepatocarcinogens. Accordingly, it has been advanced that these agents may act as tumor-promoters. These substances may also cause liver tumors in noncarcinogen-treated rodents, particularly in those characterized by a relatively high incidence of 'spontaneous' liver tumors. Since many of these chemicals are in common use, a crucial question would seem to be whether these effects are due to facilitation of the expression of pre-existing oncogenic potential. As a result of mechanistic differences tumor-promotion and syn-carcinogenesis must exhibit different dose-time-response characteristics, and accordingly, it should be possible, in principle, to discriminate between these phenomena. However, since tumor manifestation periods in the required lower dose-groups are likely to exceed the animals's av life-span, this approach is not feasible unless a sensitive early marker of carcinogenic activity can be employed. There is evidence that enzyme-deficient preneoplastic areas in liver can be used for this purpose. A strong quantitative correlation between carcinogen dose, the extent of enzyme deficient areas, and the subsequent appearance of tumors has now been established for a number of hepatocarcinogens, including those with weak initiating potential. On the basis of such quantitative analyses of the pre-neoplastic response several lines of evidence will be presented to indicate that liver-enlarging drugs do not act like solitary carcinogens, but function by facilitating the expression of carcinogenic potential. (no Refs)

21. COMPARISON OF HEPATIC CARCINOGEN INITIATION-PROMOTION SYSTEM (MEETING ABSTRACT).

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Toxicologist; 1(1):154 1981

A number of model systems have been designed to study the initiating and promoting phases of neoplastic development in rat liver. The purpose of these experiments was to determine if the promoting protocols alone altered liver biochemistry. Four protocols, which use the same initiator, diethylnitrosamine (DEN), but different promotional regimens, were investigated. The biochemical parameters evaluated were hepatic microsomal benzphetamine-N-demethylase (BPND), epoxide hydratase (EH), cytosolic DT-diaphorase, serum glutamic pyruvic transaminase (GPT) and serum gamma glutamyl transpeptidase (GGT) activities. The effect of initiation in these protocols was also evaluated to ascertain if DEN caused changes in liver biochemistry and if these changes were related to preneoplastic lesions. All 4 promoting regimes depressed BPND (20-50% of control) and all except one increased EH and DTD (3-fold). SGGT was elevated by all protocols (10x) but SGPT was only slightly changed. The combination of DEN initiation with promotion increased hepatic GGT positive foci (identified histochemically) but did not alter the biochemical parameters studied. We conclude that measurement of these enzymes is of no value for predicting neoplastic change. However, the data show that liver biochemistry, especially with respect to drug metabolism, is extensively altered by the promotional regimes. Consequently, study of promoter-induced changes in drug metabolizing enzymes may lead to a better understanding of biochemical events during promotion in hepatocarcinogenesis. (4 Refs)

22. CARCINOGENIC INITIATION AS OPPOSED TO COMPLETE CARCINOGENICITY IN THE RODENT LIVER (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

It is known that 4-N-Pyrrolidinylazobenzene (4N) is a close structural analog of the rodent liver carcinogen 4-dimethylaminoazobenzene (DAB). This structural similarity led us to evaluate it for genotoxic activity in vitro. We observed activity for 4N and DAB in the BHK cell transformation assay and subsequently in the Salmonella mutation assay of Ames. By a curious chance, Scribner, Miller and Miller, probably prompted by the same structural similarity, had synthesized 4N in the 1960's and found it to be noncarcinogenic to the rodent liver using a bioassay test protocol that detected DAB as carcinogenic. These findings were only described following the publication of our observations made in vitro. The conflict that apparently exists between these data can be interpreted in two separate ways: a) Scribner et al have suggested that 4N may be a carcinogenic initiator as opposed to a complete carcinogen like DAB. They also suggested that promotion of 4N-treated rodents with phenobarbitone might lead to the production of liver tumors. b) We have evaluated the simpler concept that the activities observed for 4N in vitro define a carcinogenic potential that is not realized in vivo due to its rapid detoxification, at least in rodents. The first of these explantations implies that pure carcinogenic initiators may form a separate class of genotoxic agents from complete carcinogens and than 4N might provide a valuable model compound for the study of carcinogenic promotion in the rodent liver. The second explanation regards potential carcinogenicity as a single property that can be defined in vitro and which may or may not be expressed in vivo depending on the enzymic environments encountered by the test chemical. (no Refs)

23. COMPARISON OF VARIOUS PROMOTING AGENTS ON THE INDUCTION OF PRENEOPLASTIC LESIONS IN THE RAT LIVER (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Rats were injected ip with N-nitrosodiethylamine (DEN) or saline (control) as an initiator. Two wk after this, rats were given test compounds mixed in the basal diet or drinking water for six wk and then killed. The results show that administration of strong hepatocarcinogens such as aflatoxin B1, DEN, N-nitrosodimethylamine (DMN), 2-acetylaminofluorene (2-AAF), 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), thioacetamide, sterigmatocystin and ethionine resulted in large numbers of hyperplastic (neoplastic) liver nodules, whereas, dieldrin, dichloro-diphenyl trichloroethane (DDT), polychlorinated biphenyls, and alpha-hexachlorocyclohexane had less promoting effects. Non-hepatocarcinogens, such as N-nitrosoethylurea and 3-methylcholanthrene, also slightly enhanced the induction of hyperplastic nodules. Of the miscellaneous compounds tested, phenobarbital, deoxycholic acid and ethinyl estradiol enhanced the nodule induction. Hepatocarcinogens and chemicals with promoting activity in liver carcinogenesis gave positive results in this system. Thus our system could be used for screening hepatocarcinogens or hepatopromoters and also estimating their potency. (no Refs)

24. THE ROLE OF GROWTH OF NORMAL AND PRENEOPLASTIC CELL POPULATIONS FOR TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Studies in vivo on the mechanisms of tumor promotion provided the following results: 1) All liver tumor promoters identified so far stimulate growth of normal liver. 2) Hepatocytes in foci or islands of altered cells (putatively preneoplastic equals pn) show higher rates of replication than normal liver cells; various different liver tumor promoters cause a further increase of proliferation of focal cells. The increased proliferative activity is found in different island phenotypes and thus seems to be a useful marker of the putative preneoplastic state. 3) Early pn foci grow slowly without promotion despite the relatively high rates of cell replication. Promoters seem to accelerate island enlargement by increasing cell replication and decreasing cell necrosis. Tumor promotion thus appears to result from events that in principle are well known to occur in normal liver. 4) Putative pn foci of unknown ('spontaneous') origin are frequent in the liver of aged Wistar rats. They are morphologically and functionally (increased proliferation) very similar to those induced by carcinogens and are responsive to tumor promoters. Promotion of these 'spontaneous' foci may explain tumor appearance after long-term application of promoters. (no Refs)

25. THE ROLE OF ESTROGEN IN HEPATIC NEOPLASIA: AN EXPERIMENTAL MODEL (MEETING ABSTRACT).

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Gastroenterology; 80(5,part2):1354 1981

The administration of estrogens to humans has been associated with the development of benign and malignant hepatocellular neoplasms. We present here a rat model which demonstrates that stilbestrol (DES) promotes the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Thirty-two male rats (Fisher 344) were given a single dose of DEN (200 mg/kg, ip) followed 4 wk later by DES (5 mg, po) twice weekly for up to 50 wk. Other rats given vehicle only served as controls. DES was stopped at the time of sacrifice or 11-29 wk prior to sacrifice. All rats given both DEN and DES developed grossly visible hepatic hyperplastic nodules, measuring up to 29 mm in diameter, after 20 wk of DES. Rats given DEN alone or DES alone did not develop nodules. Microscopic hyperplastic foci also developed in rats given DEN plus DES or DES or DEN alone. The foci developing in rats given DES were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinylestradiol (0.2 mg twice weekly) in male rats and of DES in female rats was observed. The data indicate that estrogens promote neoplasia, perhaps by increasing hepatocytic mitotic activity thereby allowing previously initiated cells to evolve into neoplastic clones. Although comparison with human disease should be made with caution, the parallels to human oral contraceptive-associated hepatic adenomas and carcinomas is obvious. It is possible that some women have latent 'initiated' cells that are unusually responsive to estrogen. (no Refs)

26. ORAL CONTRACEPTIVE STEROIDS AS PROMOTERS AND COMPLETE CARCINOGENS FOR LIVER IN FEMALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Recent reports have described an increased incidence of adenomas and hepatocellular carcinomas in livers of women with a history of long-term oral contraceptive use. Evidence derived from human and experimental animal data suggests that oral contraceptive steroids may be liver tumor promoters. Studies being carried out in my laboratory were designed to determine whether two oral contraceptive steroids, mestranol and norethynodrel, can promote diethylnitrosamine (DEN)-initiated hepatocarcinogenesis. Studies have also been conducted to determine whether these agents exhibit any detectable genotoxic effects on liver cells which would indicate that they are capable of initiating hepatocarcinogenesis. In the studies designed to detect the promoting potential of these agents, female Sprague-Dawley rats were partially hepatectomized and treated with DEN 24 hr later to initiate hepatocarcinogenesis. Twenty-four hr after injection the animals were transferred to diet containing the agent to be tested. In two separate experiments, animals were killed after 4, 9 and 12 mo of feeding diets containing the oral contraceptive steroids. Both intact animals and hepatocytes in primary culture were employed in studies designed to detect the ability of the oral contraceptive steroids to cause genetic damage in liver cells. Genotoxicity was assessed by using techniques to detect DNA damage either directly or indirectly. The results from all of these studies indicate the following: 1) mestranol and norethynodrel can promote DEN-initiated hepatocarcinogenesis as indicated by increased numbers of gamma-glutamyl transpeptidase positive, putative preneoplastic lesions after 4 and 9 mo and possibly adenomas and carcinomas after 12 mo; 2) mestranol appears to cause alterations in DNA as detected using alkaline elution; however, this is not reflected by the occurrence of detectable levels of DNA repair. (1 Ref)

27. EFFECT OF THE TUMOR PROMOTER PHENOBARBITAL ON MEMBRANE-MEDIATED PROPERTIES OF ADULT RAT LIVER-DERIVED EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT).

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In Vitro; 17(3):224 1981

We have reported a promoting action of phenobarbital on the transformation of adult rat liver (ARL) epithelial cells in culture. We report here various other biological effects of phenobarbital (PB) which mimic induction of transformation on ARL cells. A clonal line of ARL cells, which was proved to be nontumorigenic when examined for transformation markers, was seeded at a density of 1.2 x 10(4) cells/cm2 in Williams Medium E supplemented with heat-inactivated fetal bovine serum at 10% (WME:HIFBS(10)) with gentamicin at 50 ug/ml. Cells were fed with WME:HIFBS10 containing 10(-4) M PB 2 x a wk starting 24 hr after seeding and subcultured once a wk at the same seeding density. Cells that received multiple treatments of PB showed a 10-20% increase in cell population at each subculture up to 10 treatments, and continued to increase in 2-Deoxy-D-glucose (2DG) uptake in the absence of PB by as much as 77% after 2 2 treatments. On the other hand, single PB treatment of ARL cells did not enhance 2DG uptake. Neither single nor multiple treatments with PB induced anchorage independency in ARL cells. It is suggested that the alteration of plasma membrane properties by PB, as in vivo could be the mechanism of the tumor promoting activity of PB. (2 Refs)

28. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYLACETAMIDE-INDUCED RAT LIVER LESIONS.

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Gan; 72(5):798-801 1981

The enhancing effects of phenobarbital (PB) and barbital on hepatotumorigenesis were compared by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats, 2 mo old, were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. The remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% barbital diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin stained or iron stained specimens per cm2 of the liver space at 16 wk in Group I was much lower than that at termination of FAA feeding. However, the numbers of Groups II and III were well maintained at 8 and 16 wk and those at 16 wk in both groups were significantly higher than that in Group I (p less than 0.001). These data show that barbital could be an enhancer of hepatotumorigenesis like PB. (Author abstract) (25 Refs)

29. MODULATION OF TUMOR PROMOTION IN LIVER CARCINOGENESIS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Earlier, we demonstrated that feeding to rats a diet devoid of choline, a lipotrope factor, markedly enhances hepatoma induction by several chemical carcinogens, and that the diet acts as a strong promoter of liver carcinogenesis. Several modulating factors, which influence the efficacy of the choline-devoid (CD) diet as a promoter, were investigated by quantitating the evolution of initiated liver cells to foci of - glutamyltranspeptidase-positive hepatocytes. The addition to the CD diet of phenobarbitol (PHB) resulted in a promoting action stronger than those of the CD diet or PHB alone. Two structurally similar barbiturates, amobarbital and pentobarbital exerted an effect similar to that of PHB, while barbituric acid, the basic moiety of barbiturates, had no effect. In other studies, lowering of the fat con tent of the CD diet reduced its efficacy as promoter, while the addition of a hypolipidemic agent, BR931 4-chloro-6-(2,3 xylidino)-2-pyrimidinylthio(N-B-hydroxy ethyl) acetamide completely abolished the promoting action of the CD diet. Feeding the CD diet caused a marked enhancement of liver DNA synthesis and cell proliferation relative to those in rats fed the choline supplemented diet. The effects of various modulating factors on the CD diet mediated cell proliferation are being studied, and the possible significance of liver cell proliferation as a mechanism of tumor promotion will be discussed. (no Refs)

30. THE EFFECT OF A HIGH FAT DIET ON MICE BEARING LIVER TUMORS (MEETING ABSTRACT).

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Proceedings of the 35th Annual Meeting of Japanese Society of Food and Nutrition held in Tokushima, Japan, 28-30 May, 1981. Japanese Society of Food and Nutrition, Tokyo 113, Japan, 187 pp., 1981.

Mice were given commercial powdered feed to which 30% safflower oil (Group S) or margarine made of the safflower oil (Group M) had been added (both controls) for 13 mo or these diets containing 0.03% 2,7-acetylaminofluorene (AF) for 6 mo followed by the respective diets deprived of AF (group S + AF, group M + AF). They were killed after overnight fasting, the liver tumors were confirmed histologically, and the lipid concentration in their blood was measured. Liver tumors were produced in 1/13, 0/14, 8/18 and 9/15 of the rats in Groups S, M, S + AF and M + AF, respectively. Histologically, all of the tumors were nodular hyperplasia. The ratio of Type I and Type II nodular hyperplasia was 7:1 and 3:7 for groups S + AF and M + AF, respectively, the incidence of Type II nodular hyperplasia being significantly higher for group M + AF. The av concentrations of total cholesterol and triglycerides were respectively 142 and 102 mg/dl (12 mice) for Group S, 110 and 104 mg/dl (12 mice) for the mice in Group M, 116 and 90 mg/dl (10 mice) for the mice in Group S + AF without tumors, 154 and 73 mg/dl (8 mice) for the mice in Group S + AF with tumors, 122 and 124 (6 mice) for the mice in Group M + AF without tumors and 219 and 112 mg/dl (9 mice) for the mice in Group M + AF with tumors. The cholesterol values for the mice given safflower oil were significantly higher than those for the mice given margarine. There was no change in the concentration of cholesterol with tumor bearing in the mice given safflower oil, but the concentration was markedly increased by tumor bearing in the mice given margarine. The concentration of triglycerides was lowered by bearing liver tumors in the mice given safflower oil but did not change in the others. (no Refs) (In JPN)

31. ENHANCING EFFECTS OF DIMETHYLNITROSAMINE ON AFLATOXIN B1 HEPATOCARCINOGENESIS IN RATS.

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Int J Cancer; 28(5):621-626 1981

In a study of possible enhancing effects of dimethylnitrosamine (DMN) on aflatoxin B1 (AFB1) hepatocarcinogenesis, male Buffalo strain rats were fed diets containing 1 ppm AFB1, 25 ppm DMN, and a combination of 1 ppm AFB1 and 25 ppm DMN (AFB1 + DMN). The diets were replaced by chow pellets after 6 mo, and animals were killed 3, 6, 9 and 12 mo after the onset of the experiment. In the untreated control group animals were free of hepatocellular carcinoma but the treated groups fed AFB1, DMN and AFB1 plus DMN developed hepatic lesions ranging from multiple cysts, altered cell foci and neoplastic nodules to hepatocellular carcinomas. Hepatocellular carcinomas developed in 79%, 45% and 5% of rats fed AFB1 plus DMN, AFB1 and DMN respectively at the end of the experiment. Multiple cysts were also found in all periods in animals fed AFB1 plus DMN, whereas rats fed AFB1 and DMN separately developed a few multiple cysts by the end of the experiment. These findings suggest that DMN potentiates the hepatocarcinogenesis induced by AFB1 in rats. (Author abstract) (28 Refs)

32. ENHANCED SUSCEPTIBILITY TO AFLATOXIN B1 TOXICITY IN WEANLING MICE PRETREATED WITH CARBON TETRACHLORIDE.

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Acta Pathol Microbiol Scand [A]; 89(4):303-308 1981

Weanling male mice with or without prior treatment with CCl4 (0.5 ml/kg) were exposed to either single (20.5, 25.6, 32 and 40 mg/kg) or multiple (4 mg/kg for 10 days or 8 mg/kg for 5 days) doses of aflatoxin B1. Evidence of its acute toxic and carcinogenic effects was found only in CCl4 pre-treated mice. Single dose LD 50 value under these conditions was calculated to be 26.8 mg/kg. Histological changes which predominantly occurred in the liver were characterized by acute necrosis and degeneration of the parenchymal cells. Hepatomas were observed as early as 9 mo of age in CCl4 pre-treated animals given 4 mg/kg aflatoxin daily for 10 days. It is thus suggested that the repeated use of CCl4 as an anthelmintic in animals which are apparently resistant to the lethal and hepatocarcinogenic action of aflatoxin might increase their sensitivity to this mycotoxin. (Author abstract) (20 Refs)

33. COCARCINOGENICITY BY SACCHARIN OF HEPATOCARCINOGENICITY (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We have demonstrated that sodium saccharin was cocarcinogenic towards dibutylnitrosamine (DBN) hepatocarcinogenesis. The simultaneous administration of 5% sodium saccharin in the diet and 0.02% DBN in the drinking water of male rats for 26 wk resulted in a significant increased incidence of preneoplastic foci, hyperplastic nodules and hepatocellular carcinomas compared to rats that received only DBN. The liver of the rats receiving both DBN and saccharin also had an increased incidence of gammaglutamyltranspeptidase (GGTase) positive foci after 4, 8 and 26 wk of treatment. The size distribution of the GGTase-positive foci was the same in the livers of the DBN and DBN-saccharin groups. The livers from rats that only received saccharin did not contain GGTase-positive foci but rather contained at 4 to 8 but not 26 wk a large number of GGTase-positive hepatocytes in Zone 1. It would appear that by 26 wk of saccharin treatment the liver may have developed resistance to saccharin. Our results indicate that the mechanism for the cocarcinogenic activity of saccharin involves an increase in the amount of initiated GGTase-positive foci, and by implication initiation sites of carcinogenesis rather than an increased growth rate of GGTase-positive foci. This implies that the cocarcinogenic activity of saccharin in the liver involves a mechanism different from tumor promoters which act to increase the rate of progression (growth) from the initiated cell to the appearance of cancer. (no Refs)

34. EFFECTS OF CADMIUM IN VITRO ON BENZO(A)PYRENE METABOLISM BY RAT TESTICULAR AND HEPATIC MICROSOMES (MEETING ABSTRACT).

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Toxicologist; 1(1):121 1981

Cadmium is known to have toxic effects on the testes as well as to inhibit microsomal mixed function oxidase activity in a variety of tissues. Studies were carried out to compare the actions of cadmium in vitro on testicular and hepatic metabolism of benzo(a)pyrene (BP), a compound which requires metabolic activation for its mutagenic and carcinogenic effects. Testicular and hepatic microsomes were obtained from normal male rats and incubated with BP in the presence of saturating concentrations of NADPH and varying (2 x 10(-4) M -5 x 10(-6) M) concentrations of cadmium. In liver microsomes, cadmium produced a dose-dependent decrease in the production of fluorescent metabolites (phenols). By contrast, in testicular microsomes, the lower concentrations of cadmium (2.5 and 5 x 10(-5) M) enhanced the formation of phenols whereas higher levels (greater than 1 x 10(-4) M) decreased the production of fluorescent metabolites. To determine if the changes in testicular production of phenolic metabolites might be related to alterations in competing metabolic pathways, the effects of cadmium on the activity of epoxide hydrase, an enzyme required for the production of dihydrodiol metabolites, were investigated. Cadmium produced a dose-dependent inhibition of epoxide hydrase activity in both testicular and hepatic microsomes. The effects in testes were greater than those in liver. Preliminary analysis of BP metabolites by high performance liquid chromatography further indicates that cadmium affects the production of both phenols and dihydrodiols by testicular and hepatic microsomes. The results demonstrate that cadmium alters the routes of metabolism of BP in the testes and may therefore, influence its toxicity. (no Refs)

35. SURFACE ACTIVE AGENTS AS TUMOR PROMOTERS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Initiation and promotion are different stages in carcinogenesis. Initiators are generally mutagenic and if a substance or procedure is carcinogenic and not mutagenic the effect is most probably tumor promotion. Many carcinogens are complete, having both initiating and promoting activity. Promoters alone induce tumors because initiators are present in the diet or the environment. Promoters can be physical as with trauma and foreign bodies such as with asbestos. Promoters are often organotropic; phenobarbitone, clofibrate and valium act on the liver of rodents. Of the 14 types of tumor promoters listed, the class of surfactants includes many different compounds. Saccharin, cyclamate and tryptophan act on the rat bladder, and lithocholic acid on the colon. The sweetening agents and bile acids reduce interfacial tension by some 20% in concentrations at which they are present in urine or feces when given in doses which promote tumors in rats. The incidence of cancer of esophagus and mouth is high in smokers who consume spirits rather than beer. The cigarette provides initiators and the alcohol acts as promoter. The alcohol present in spirits would reduce the interfacial tension appreciably in the mouth and esophagus so that the carcinogenic action of spirits is probably due to the promoting action of the alcohol because of its surface activity. With promoters of the surfactant type there are levels below which the effects are negligible and so there may be safe levels. This is clearly the concentration attained at any particular time rather than the total dose. The effect of the surface active tumor promoters is probably due to action on cell membranes. The mode of action of solvents such as chloroform and benzene is probably similar. There must be safe or threshold levels for the surface active and other promoters, but probably not for materials like asbestos which remain in the body. It is possible that there are no safe levels for initiators, but if there were they might vary with exposure to promoters. (no Refs)

36. MODIFICATION OF HEPATOTOXIC EFFECT OF HALOGENATED HYDROCARBONS ON PARTIALLY HEPATOECTOMIZED RATS.

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Toxicol Eur Res; 3(4):197-200 1981

The effect of hepatectomy on the hepatotoxic effect of halogenated hydrocarbons was studied. Male rats received po administration of chloroform or carbon tetrachloride at a single dose of 500 mg/kg, 3 days prior to or after the partial hepatectomy. The hepatotoxic effect of the toxins was modified in a different manner according to the time of the hepatectomy. In the animals hepatectomized 3 days after the hepatotoxin administration, histological changes of the liver were similar to those of the non-hepatectomized rats, except with an increase in the activity of GOT and GPT. On the contrary, in the animals hepatectomized 3 days prior to hepatotoxin adminstration, the toxic effect of the chemicals was less enhanced than in the non-hepatectomized animals. (Author abstract) (12 Refs) (In FRE)

37. BUTYLATED HYDROXYTOLUENE PRETREATMENT REDUCES CYTOTOXICITY AND COVALENT BINDING OF AFLATOXIN B1 IN PRIMARY HEPATOCYTE CULTURES (MEETING ABSTRACT).

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Toxicologist; 1(1):108 1981

Primary cultures of adult rat hepatocytes were used to characterize the effect of butylated hydroxytoluene (BHT) pretreatment on the cytotoxicity and metabolism of a cytotoxic dose of aflatoxin B1 (AFB1). Male Sprague-Dawley rats were divided into two groups of four each, and fed either a control diet or one containing 0.5% BHT. After ten days, hepatocytes were prepared and cultured in chemically-defined, hormone-supplemented medium. After 20-22 hr in culture, 0.12-0.15 ug of [14C] AFB1 were added to dishes containing 2.5 x 10(6) cells. Medium was removed from sets of three cultures at 1/2, 1, 2, 4, 6, 10, and 24 hr thereafter, and extracted with chloroform. Cells were precipitated with 5% TCA and washed exhaustively with organic solvents. After 10 hr, control cells converted 59% of the AFB1 to aqueous metabolites, while 15% was bound covalently. During the same intervals, cells from BHT-fed rats produced 69% aqueous metabolites, and only 6% was bound covalently. AFB1-induced cytotoxicity was much greater in cells from control rats, as evidenced by release of lactate dehydrogenase (LDH) into the medium. Thirty-one hr after addition of AFB1, LDH levels in media from control cells av 1036+/-169 units/ml, while media from BHT-pretreated cells contained only 350+/-45 units/ml. BHT reduces cytotoxicity by apparently increasing the output of relatively nontoxic, water-soluble metabolites and decreasing the output of activated metabolites which covalently bind to macromolecules. Based on results from this in vitro model, we predict the BHT will also protect against AFB1-induced acute toxicity and carcinogenicity in vivo. (no Refs)

38. THE EFFECT OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF THE HEPATOCARCINOGEN 2-ACETYLAMINOFLUORENE IN THE RAT.

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Diss Abstr Int [B]; 42(4):1412-B 1981

Hepatic enzymes, presumably involved in the metabolism of the hepatocarcinogen 2-acetylaminofluorene (AAF), were examined in rats fed a Torula yeast-based selenium-deficient diet or the same diet supplemented with 0.5 ppm selenium (as sodium selenite). Selenium-deficient rats exhibited almost total absence of hepatic selenium-dependent glutathione peroxidase activity three wk after initiation of test diet feeding. Dietary selenium had no significant effect on hepatic soluble sulfotransferase activity in vitro as measured with the substrates, N-hydroxy-AAF and phenol. Hepatic lipid peroxidation (HLP) was not altered by AAF-challenge in rats fed either diet. In agreement with previous reports, dietary selenium protected against increased HLP produced by administration of carbon tetrachloride. Selenium-supplemented rats exhibited (a) no significant change in the production of 7-,5-, and N-hydroxy-AAF metabolites and (b) significantly increased production of 3-hydroxy-AAF metabolite as compared to selenium-deficient rats. Dietary selenium had no significant effect on total metabolites excreted or on the major phenolic metabolites excreted into the free-glucosiduronic acid-conjugated, or sulfuric acid-conjugated fractions. However, selenium-deficient rats excreted two and three x more N-hydroxy-AAF into the free-, and glucosiduronic acid-conjugated fractions, respectively. These findings tend to support the hypothesis that dietary selenium alters the in vivo metabolism of AAF in a manner that selectively decreases N-hydroxy-AAF excretion, and possibly its production. Thus dietary selenium's protective effect against AAF-induced hepatocarcinogenesis may be partially explained by the ability of selenium to decrease the amount of N-hydroxy-AAF available for further activation. (no Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

39. IN VITRO METABOLISM OF ACRYLONITRILE TO 2-CYANOETHYLENE OXIDE, REACTION WITH GLUTATHIONE, AND IRREVERSIBLE BINDING TO PROTEINS AND NUCLEIC ACIDS.

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Cancer Res; 41(12):4925-4933 1981

The metabolism of the suspected carcinogen acrylonitrile was studied using subcellular fractions isolated from rats and humans. Irreversible binding of radioactive label from [1-14C]- or [2,3-14C]acrylonitrile to protein and DNA was enhanced by reduced nicotinamide adenine dinucleotide phosphate in the presence of rat liver microsomes or a reconstituted cytochrome P-450 system. During the reduced nicotinamide adenine dinucleotide phosphate-dependent reaction, HCN was produced, and the heme of cytochrome P-450 was destroyed. Rat brain microsomes did not produce detectable levels of metabolites. Conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems was not found. With rats, metabolism was induced by pretreatment of animals with either phenobarbital or 5,6-benzoflavone. Labeled 2-cyanoethylene oxide was found to bind irreversibly to calf thymus DNA and microsomal protein. The extent of binding was greater in the case of 2,3-14C-labeled than 1-14C-labeled material. The relative first-order rate of acrylonitrile binding to calf thymus DNA in rat liver microsomal systems was one to two orders of magnitude less than that for 1,1,2-trichloroethylene and three orders of magnitude less than that for vinyl chloride or vinyl bromide. Rat liver microsomes or a reconstituted cytochrome P-450 system catalyzed the mixed-function oxidation of acrylonitrile to 2-cyanoethylene oxide. 2-Cyanoethylene oxide has a half-life of about 2 hr in neutral buffer at 37 C. This epoxide was found to serve as a substrate for microsomal epoxide hydrolase. HCN was released during hydrolysis of 2-cyanoethylene oxide or reaction of the epoxide with reduced glutathione; however, HCN release in either case was not stoichiometric with epoxide disappearance. 2-Cyanoethylene oxide reacted less rapidly with reduced glutathione than did acrylonitrile. Rat liver cytosol preparations contained glutathione S-transferase activity towards acrylonitrile and greater activity with 2-cyanoethylene oxide as a substrate. Cytosol preparations from rat brain and human liver had no detectable glutathione S-transferase activity towards acrylonitrile but did exhibit some activity towards 2-cyanoethylene oxide. These studies establish the basic pathways involved in the metabolism of acrylonitrile and should provide a basis for examination of the relevance of these individual steps and their roles in bioactivation and detoxication under more physiological situations. (Author abstract) (40 Refs)

40. EFFECTS OF CARCINOGENS, MUTAGENS, AND TERATOGENS ON NON-HUMAN SPECIES-AQUATIC ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP
United States Environmental Protection Agency, Gulf Breeze, FL
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Aquatic systems and organisms are under both laboratory and field study in order to develop indicator, screening, and modeling capabilities for detection and evaluation of risks of carcinogens, mutagens, and teratogens. In the third yr of the program, several advances were made in the development of minnow (liver lesions via benzidine and aflatoxin exposures), rainbow trout (liver tumors via benzo(a)pyrene (B(a)P) exposures), and freshwater catfish (papillomatous-like lesions via chlorinated effluent exposures). A novel approach has shown that tiger salamanders may be good biochemical and histologic indicators of the presence of certain carcinogens (polycyclic aromatic hydrocarbons-PAH's). The skin and liver tissues of the salamanders revealed induced enzyme activity following exposure to the PAH, perylene. Considerable field monitoring work on mollusks and carcinogenic PAH's along the coast of Oregon has revealed a positive correlation between prevalence of cellular proliferation disorders in shellfish and higher concentrations of certain PAH's in natural water. Emphasis in biochemistry for the last yr has been directed mostly toward the elucidation of the metabolisms of the mixed-function oxidases in marine organisms. From continuing work on the mullet (Mugil cephalus), we have found that benzo(a)pyrene is converted mainly to 3-hydroxybenzo(a)pyrene, 9-hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-dihydroxydiols of B(a)P, in in vitro systems containing liver microsomes from Aroclor 1254-treated mullet. Other metabolites such as diones of B(a)P and probably tri- and tetraols have also been produced. We have also developed a procedure for the epoxide hydrolase enzyme system in order to determine the role of this enzyme on the metabolism of the polyaromatic hydrocarbons. These studies continue to reveal that fish have similar metabolic pathways to mammals for disposition of certain carcinogens. (no Refs)

41. ACTIVATION OF N-2-ACETYLAMINOFLUORENE BY TARGET AND NONTARGET SYRIAN GOLDEN HAMSTER CELLS (MEETING ABSTRACT).

Poiley JA, Raineri R, Ernst MK, Andrews AW, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability to metabolize and activate N-2 acetylaminofluorene (AAF) of Syrian golden hamster kidney, bladder, small intestine, lung and liver cells was compared with that of hamster embryo fibroblasts. At varying times after isolation, cells were exposed to 5 ug [14C]-AAF for 3, 6 or 24 hr. The level of AAF remaining and the amount bound to cellular components were determined. Within 3 hr, hepatocytes and intestinal cells had metabolized 95% of the AAF. Within 6 hr lung cells had metabolized 50%, and kidney cells 20%. By contrast, fibroblasts and bladder cells had metabolized only 20-25% in 24 hr. The amount of material bound to cellular components was proportional to the amount of AAF metabolized. A second measure of activation was the ability of intact organ cells to metabolize AAF to a form mutagenic in Salmonella TA 1538. Revertant numbers were much increased above background with hepatocytes (240-fold), lung cells (11-fold), intestinal cells (5-fold) and kidney cells (2-fold). With bladder cells and fibroblasts, revertant numbers were not significantly higher. We have demonstrated that intact cells, whether or not from the target organ, can metabolize AAF at a high rate to forms which either bind to cellular components or are excreted. These forms are also mutagenic in Salmonella. (no Refs)

42. SULFATE-DEPENDENT METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY PRIMARY CULTURES OF ADULT RAT HEPATOCYTES (MEETING ABSTRACT).

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Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):35 1981

The role of sulfate in the metabolic activation of the model aromatic amine hepatocarcinogen 2-acetylaminofluorene (2AAF) was determined using primary hepatocyte cultures as a cellular model of the liver. Adult male rat hepatocytes were isolated by collagenase perfusion of the liver and maintained in collagen-coated dishes with hormone-supplemented, chemically defined media. Cytochrome P-450 levels were fully maintained in the cultures for 48 hr. After 28 hr, the cultures were incubated with 67-137 ng of [14C]2AAF. Polar metabolites were isolated by chloroform-water partitioning, and bound carcinogen residues were measured as non-extractable radioactivity incorporated into hepatocellular trichloroacetic-acid-insoluble material. In an experiment using sulfate-free medium, sulfate supplementation doubled the level of bound residues at 2 and 3 1/2 hr but had no effect at 21 hr. Culture media containing 0, 0.1, 0.5 and 1.0 mM sulfate respectively produced 0.8, 1.4, 3.6 and 4.8% bound residues in a 3 hr incubation. Sulfate supplementation did not effect the overall rate of 2AAF metabolism. Phenol, at 1 uM in sulfate-free media, doubled the level of bound residues. Galactosamine, at 2mM, reduced by half the level of bound residues in cultures incubated with 2AAF and 1mM sulfate. These findings support the importance of sulfoconjugation in the metabolic activation of 2AAF. (no Refs)

43. ACTIVATION AND DETOXIFICATION OF BENZO(A)PYRENE BY HAMSTER AND RAT HEPATOCYTES (MEETING ABSTRACT).

Raineri R, Poiley JA, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability of hepatocytes from Syrian golden hamsters and Sprague-Dawley rats to metabolize and covalently bind [3H]-benzo(a)pyrene (BP) was examined. Following 3 hr incubation with 4.4 uM BP, hamster hepatocytes metabolized 95% of the BP; rat hepatocytes only 41%. There were 5 x more water-soluble metabolites in the medium from hamster than from rat hepatocytes. The levels of organic solvent-soluble metabolites (OSM) were similar. While beta-glucuronidase treatment of hamster hepatocyte medium increased the OSM, no such increase was seen after treatment of rat hepatocyte medium. The results were similar after treatment with arylsulfatase. When hepatocytes from Aroclor 1254 (AC)-treated animals were compared, increases in OSM after enzymatic deconjugation occurred only with hamster preparations. A 5-fold increase in levels of binding of BP to hamster hepatocyte RNA, and a 17-fold increase to rat RNA, occurred when hepatocytes from AC-treated animals were used. Increased levels of binding to rat hepatocyte DNA and protein were also seen. Although BP is not considered a liver carcinogen, we found high rates of conjugation and binding in liver cells. Initial metabolism may therefore occur in the liver followed by transport of conjugated metabolites and subsequent activation at the site of tumor induction. (no Refs)

44. THE INFLUENCE OF POLYCYCLIC AROMATIC HYDROCARBONS AS INDUCERS OF MONOOXYGENASES ON THE METABOLITE PROFILE OF BENZ(A)ANTHRACENE IN RAT LIVER MICROSOMES.

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Cancer Lett; 14(2):175-185 1981

Changes in metabolite profiles resulting from induction of monooxygenases by polycyclic aromatic hydrocarbons (PAH) in Wistar rats is reported. Benz(a)anthracene (BA) was used as substrate. Rat liver microsomes converted BA preferentially into 5,6-, 8,9-, and 10,11-trans-dihydrodiols. With control microsomes, approx 5x more 10,11-trans-dihydrodiol than 5,6-and 8,9-dihydrodiol was formed. All tested inducers increased the epoxidation at the 5,6-position and to a lesser extent at the 8,9-position. Oxidation at the 10,11-position, however, was decreased after almost all inducers. Treatment with more effective inducers resulted in an increased secondary metabolism, especially the formation of the bay-region dihydrodiol epoxide. While phenobarbital and the moderately-inducing PAH induced oxidation at the 5,6-and 8,9-positions, other compounds, especially the benzofluoranthenes, also induced oxidation at the 3,4-position. This reaction leads to formation of the ultimate carcinogen of BA, 3,4-dihydroxy-1,2-epoxy-1,2,3,4 tetrahydrobenz(a)anthracene. (35 Refs)

45. ARYL HYDROCARBON HYDROXYLASE IN ALCOHOLIC CIRRHOSIS AND PRIMARY BILIARY CIRRHOSIS (MEETING ABSTRACT).

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Department of Medicine (Geriatrics), The University, Newcastle upon Tyne, England
Gut; 22(5):A419 1981

Aryl hydrocarbon hydroxylase (AHH) is involved in the transformation of polycyclic hydrocarbons to carcinogenic metabolites. In animals, hepatic AHH activity is a major determinant of the carcinogenicity of polycyclic hydrocarbons. Because the occurrence of primary liver cancer in patients with primary biliary cirrhosis is strikingly lower than in alcoholic cirrhosis, we have compared hepatic microsomal AHH activity in these two groups, and in histologically normal liver tissue obtained during diagnostic workup. Both basal and induced (after 18 hr incubation with benzanthracene) AHH activities were measured. Basal and induced AHH activity (pmol 3-OH-BP/mg protein/hr) was 95.2 +/-10.3 and 152 +/-22 in normal biopsies compared with 54.7 +/-4 and 122 +/-11 in alcoholic cirrhotics and 28.2 +/-3 and 55 +/-7 in primary biliary cirrhosis. AHH activity in both cirrhotic groups was significantly lower (p less than 0.01) than in normal patients, and the activity in primary biliary cirrhosis was significantly less (p less than 0.001) than in alcoholic cirrhosis. These differences remained significant when smokers and women were considered as separate groups. These results suggest that (1) although AHH may play a role in the pathogenesis of primary liver cancer in alcoholic cirrhosis, other factors must be involved; (2) this potential impairment in production of carcinogenic metabolities in primary biliary cirrhosis may offer some explanation for the low incidence of primary liver cancer in this group. (no Refs)

46. ENZYME INDUCTION AND HEPATIC GLYCEROLIPID SYNTHESIS IN RATS TREATED WITH 3-METHYLCHOLANTHRENE.

Goldberg DM, Roomi MW, Yu A, Roncari DA
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Can J Biochem; 59(9):793-798 1981

Fasting male rats fed 3-methylcholanthrene in a daily dose of 40 mg/kg body wt-1 gave evidence of hepatic microsomal enzyme induction after 3 days through significantly increased hepatic aryl hydrocarbon hydroxylase activity, cytochrome P448 content, and characteristic changes in microsomal proteins analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Concomitantly, activities of aminopyrine N-demethylase and microsomal gamma-glutamyltransferase, which are increased in phenobarbital-treated rats, significantly declined. In contrast to phenobarbital, which has been previously shown to increase hepatic triacylglycerol content and in vitro glycerolipid synthesis, 3-methylcholanthrene did not affect hepatic triacylglycerol content, but did inhibit glycerolipid synthesis by cell-free preparations of rat liver and significantly reduced serum triacylglycerol concentration. Thus, the two prototypical drugs inducing characteristically different changes in microsomal enzyme and hemoprotein response also seem to differ in their effect upon another important microsomal function, hepatic glycerolipid synthesis. (Author abstract) (31 Refs)

47. LUNG AND LIVER CELL-MEDIATED MUTAGENESIS SYSTEMS: SPECIFICITIES IN THE ACTIVATION OF CHEMICAL CARCINOGENS.

Langenbach R, Nesnow S, Tompa A, Gingell R, Kuszynski C
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Carcinogenesis; 2(9):851-858 1981

Carcinogens from three chemical classes were compared for mutagenicity in systems containing cocultivated adult Sprague Dawley rat hepatocytes or lung cells and Chinese hamster V79 cells. 7,12-dimethylbenz[a]anthracene (DMBA), 3-methylcholanthrene (MCA), and benzo[a]pyrene (BP) were mutagenic for V79 cells in the lung cell-mediated system. DMBA and MCA were less mutagenic in the liver system, and BP was negative in this system. Aflatoxin B1 was mutagenic in the liver cell system but was only weakly mutagenic in the lung cell system. Dimethylnitrosamine (DMN) was mutagenic only in the presence of liver cells. The metabolism of BP and DMN was investigated to gain insight into the causes of their organ specificity. For DMN, the lack of metabolic activation by rat lung cells apparently accounted for its lack of mutagenicity in the lung cell-mediated system. BP was metabolized by both systems, but quantitative differences were observed in the metabolites detected. Lung cells produced primarily the 7,8-and 9,10-diols and little detectable 4,5-diol, whereas liver cells produced the 4,5-diol as the major metabolite. (38 Refs)

48. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE AND 3,3,5,5-TETRADEUTERO-N-NITROSOMORPHOLINE IN THE F344 RAT.

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Div. Chemical Carcinogenesis, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Cancer Res; 41(12):5039-5043 1981

We studied the metabolism in the male F344 rat of N-nitrosomorpholine and of 3,3,5,5-tetradeutero-N-nitrosomorpholine; the latter is less carcinogenic and less mutagenic than is N-nitrosomorpholine. Alpha-Hydroxylation (3-or 5-hydroxylation) of N-nitrosomorpholine by liver microsomes and a reduced nicotinamide adenine dinucleotide phosphate-generating system produced (2-hydroxyethoxy)acetaldehyde, which was identified as its 2,4-dinitrophenylhydrazone derivative. When we administered N-nitrosomorpholine to rats ip, we did not detect (2-hydroxyethyl)acetaldehyde in the urine, but we did identify (2-hydroxyethoxy)acetic acid (16% of the dose). We also identified N-nitroso(2-hydroxyethyl)glycine (33% of the dose) from beta-hydroxylation (2-or 6-hydroxylation), N-nitroso-diethanolamine (12%), and unchanged N-nitrosomorpholine (1.5%) in the urine. The deuterated analogs of the above metabolites were isolated from the urine of rats treated with 3,3,5,5-tetradeutero-N-nitrosomorpholine in yields as follows: (2-hydroxyethoxy)acetic acid (3.4%); N-nitroso(2-hydroxyethyl)glycine (37%); N-nitrosodiethanolamine (12%); N-nitrosomorpholine (0.4%). These data demonstrate that deuterium substitution in the alpha-positions of N-nitrosomorpholine caused a decrease in the extent of alpha-hydroxylation and indicate that alpha-hydroxylation is the mechanism of activation of N-nitrosomorpholine. (Author abstract) (31 Refs)

49. METABOLISM OF NITROSOACETOXYMETHYLMETHYLAMINE IN LIVER MICROSOMES.

Appel KE, Frank N, Wiessler M
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Biochem Pharmacol; 30(20):2767-2772 1981

The carcinogen nitrosoacetoxymethylmethylamine (NAMM) was incubated with mouse liver microsomes. The decomposition rate of NAMM and the formation of methanol were determined. After addition of an NADPH-regenerating system, formaldehyde formation resulting from metabolic degradation of the methyl group of NAMM was measured. The results suggest that NAMM is rapidly hydrolyzed by unspecific esterases to nitrosohydroxymethylmethylamine (NHMM). NHMM decomposes according to the activation mechanism of nitrosodimethylamine (NDMA). The formation of methanol proceeds with an even lower velocity. This indicates that intermediate breakdown products - probably NHMM or methyldiazohydroxide (MDH) - possess a distinct stability. Oxidative demethylation of NHMM or MDH was not detectable. The methanol formed is oxidized to formaldehyde by microsomal enzymes. (Author abstract) (31 Refs)

50. METABOLISM OF CYCLOPROPENOID FATTY ACIDS AND AFLATOXIN B1 IN ISOLATED HEPATOCYTES OF RAINBOW TROUT (SALMO GAIRDNERI) (MEETING ABSTRACT).

Taylor MJ, Bailey GS, Selivonchick DP
Department of Food Science, Oregon State University, Corvallis, OR, 97331
Toxicologist; 1(1):34 1981

Rainbow trout are the most sensitive animal to Aflatoxin B1 (AFB) hepatocarcinogenicity. AFB1 is a potent carcinogenic mycotoxin occurring in contaminated peanuts, corn, and other grains. Trout feeding studies have also demonstrated the great synergistic hepatocarcinogenicity between AFB1 and cyclopropenoid fatty acids (CPFA). CPFA occur naturally in cotton-seed, kapok, and other food oils. Reason for this synergism has been the subject of much research. Hepatocytes were isolated in high viability (90% lactic dehydrogenase retained) from rainbow trout liver in situ by a two-step collagenase perfusion. Cells were incubated with CPFA and AFB1 and various metabolic parameters assessed. CPFA caused a dose-dependent fall in cellular glutathione (GSH) level, and a concomitant rise in lipid peroxidation occurred even in the absence of added ADP-Fe. The drop in GSH content was slower with CPFA than with diethyl maleate (DEM). Great excesses of either CPFA or DEM were required to significantly decrease cellular GSH. Binding of 3H-AFB1 to DNA was also investigated. AFB1 was rapidly bound to DNA in isolated hepatocytes. A dose of AFB1 added to cells after 0,1,2,3 or 4 hr preincubation resulted in the same level of DNA binding. Benzo(a)pyrene monooxy genase activity also remained constant for 4 hr. Cytotoxicity of AFB1 and the effect of CPFA on AFB1-DNA binding will be presented. (no Refs)

51. METABOLISM AND DISPOSITION OF TRIS BP IN THE RAT (MEETING ABSTRACT).

Matthews HB, Nomeir AA
National Institute of Environmental Health Science and National, Toxicology Program Research Triangle Park, NC, 27709
Toxicologist; 1(1):35 1981

The flame retardant chemical tris (2,3-dibromopropyl)phosphate (Tris BP), has been shown to be carcinogenic in laboratory animals. In an effort to provide additional data on the disposition of Tris BP in laboratory animals the oral and dermal absorption, tissue distribution, metabolism and excretion of 14C-labeled Tris BP have been studied in the rat. The results of these studies indicate that Tris BP is readily absorbed from the gastrointestinal tract and absorbed at an appreciable rate from the skin. Following absorption Tris BP is distributed to all the major tissues, but Tris BP derived radioactivity is most concentrated in liver, blood and kidney. Tris BP is readily metabolized and excreted in the form of several polar metabolites in urine and feces and as CO2 in exhaled air. Six metabolites of Tris BP have been isolated and identified from urine and bile. Excretion of unmetabolized Tris BP is negligible. In vitro studies of Tris BP metabolism have demonstrated that enzymes in liver degrade the parent chemical to the same polar metabolites which were isolated and identified from urine and bile. The enzymes responsible for Tris BP metabolism are concentrated in microsomal and soluble portions of liver homogenates and require NADPH and glutathione, respectively, as cofactors for enzyme activity. (no Refs)

52. IN VITRO AND IN VIVO COVALENT BINDING OF THE KIDNEY TOXICANT AND CARCINOGEN TRIS(2,3-DIBROMOPROPYL)-PHOSPHATE.

Soderlund EJ, Nelson SD, Dybing E
Dept. Toxicology, Natl. Inst. Public Health, Postuttak, Oslo 1, Norway
Toxicology; 21(4):291-304 1981

Incubation of 3H-tris(2,3-dibromopropyl)-phosphate (TRIS-BP) with rat liver microsomes led to its activation to products which bound covalently to microsomal protein. The reaction was NADPH-dependent, and boiled microsomes yielded no binding. The reaction could be inhibited by nitrogen; carbon monoxide, which inhibits cytochrome P-450-mediated reactions, also reduced binding rates significantly. SKF 525-A and metyrapone, a selective inhibitor of phenobarbital-inducible cytochrome P-450, inhibited TRIS-BP activation. Alpha-napthoflavone, a selective inhibitor of cytochrome P-448, had little effect. Addition of glutathione and N-acetylcysteine markedly inhibited binding, but ascorbic acid did not. Paraoxon, an esterase inhibitor, and 1,1,1-trichloropropene-2,3-epoxide and cyclohexene oxide also were without effect. Rat kidney microsomes were capable of activating TRIS-BP to 8% of the level achieved by rat liver microsomes. Administration of TRIS-BP to rats resulted in considerable binding to kidney proteins, with lesser amounts detected in liver and very little in muscle proteins. Liver microsomes activated TRIS-BP to bind to DNA in vitro, but kidney microsomes did not. (31 Refs)

53. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE (MEETING ABSTRACT).

Hecht SS, Young R, Chen CB
American Health Foundation, Valhalla, NY, 10595
Toxicologist; 1(1):35 1981

N-Nitrosomorpholine (NM) is a potent carcinogen which induces liver tumors in rats and tumors of the trachea and nasal cavity in Syrian golden hamsters. 3,3,5,5-TetradeuteroNM is less carcinogenic and less mutagenic than NM, indicating that the metabolic activation of NM proceeds by hydroxylation of the 3 and 5 carbons (alpha carbons). However, metabolic alpha hydroxylation of NM has not been previously demonstrated. We incubated NM with rat liver microsomes and an NADPH generating system and demonstrated alpha hydroxylation by isolation of (2-hydroxyethoxy)acetaldehyde as its 2,4-dinitrophenylhydrazone (DNP) derivative. The rate of formation of (2-hydroxyethoxy)acetaldehyde in microsomal incubation mixtures can be assayed by reverse-phase high pressure liquid chromatography (HPLC) of its DNP. When rats were injected with NM, we did not detect (2-hydroxyethoxy)acetaldehyde in the urine, but we did isolate (2-hydroxyethoxy)acetic acid, which presumably resulted from further oxidation. Data will be presented on the deuterium isotope effect for alpha hydroxylation of NM and on the effects of mixed function oxidase inducers on alpha hydroxylation. (no Refs)

54. TOXICOLOGICAL IMPLICATIONS OF HEPATIC PEROXISOME PROLIFERATION IN RODENTS: POSSIBLE ROLE OF OXYGEN RADICAL TOXICITY IN HYPOLIPIDEMIC DRUG-INDUCED CARCINOGENESIS (MEETING ABSTRACT).

Reddy JK, Warren JR
Northwestern University Medical School, Chicago, IL
Toxicologist; 1(1):131 1981

The hepatomegaly induced by the hypolipidemic drugs and phthalate ester plasticizers is characteristically associated with a marked increase of peroxisomes in the cytoplasm of liver cells of rats, mice and hamsters. Peroxisomes contain catalase, several H2O(2)-generating oxidases, carnitine acetyltransferase, as well as enzymes involved in the beta- oxidation of long-chain fatty acids. The activities of these enzymes in liver are elevated in association with peroxisome proliferation. To evaluate the implications of persistent peroxisome proliferation, chronic toxicity studies were undertaken. To date, clofibrate, nafenopin, Wy-14,643, BR-931, tibric acid and methyl clofenapate, 6 structurally different peroxisome proliferators, were found to be hepatocarcinogenic in rats and/or mice. None of these compounds caused detectable mutagenic activity in the Salmonella/microsome assay or produced DNA damage in the lymphocyte [3H] thymidine incorporation asssay. The lack of mutagenicity of these compounds strongly suggests that the carcinogenicity may be related directly to peroxisome proliferation. The sustained increase in liver cell peroxisome population appears to cause an excessive generation of H2O2 as a result of increased H2O(2)-generating peroxisomal oxidases and elevated peroxisomal beta-oxidation of fatty acids. The H2O2 thus generated may react with superoxide radical to form hydroxyl radical. The rate of production of these highly toxic oxygen radicals, including singlet excited oxygen formation, and their cumulative effect on DNA, may determine the relationship between peroxisome proliferation and hepatocarcinogenicity in rodents chronically exposed to peroxisome proliferators. (no Refs)

55. METABOLISM AND MACROMOLECULAR BINDING OF THE CARCINOGEN MICHLER'S KETONE IN RATS.

Struck RF, Shih TW, Johnston TP, Kirk MC, Hill DL
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Xenobiotica; 11(8):569-577 1981

Studies on the metabolism of 14C-Michler's ketone (4,4'-bis-(dimethylamino)[carbonyl-14C]benzophenone) in rats have revealed that this carcinogen is subject to demethylation, ring-hydroxylation and N-acetylation after adjacent methyl groups have been removed. As identified by mass spectral analysis, microsomal metabolites are the mono-, di-, tri- and tetra-demethylated derivatives. The major metabolites appearing in the bile are the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound; minor metabolites, tentatively identified, are the ring-hydroxylated derivatives of di- and tri-demethylated Michler's ketone and of N-acetylated tri- and tetra-demethylated Michler's ketone. The major urinary metabolite is tentatively identified as a ring-hydroxylated derivative of N-acetylated, di-demethylated Michler's ketone; a minor urinary metabolite lacks the hydroxyl group. Injection of 14C-Michler's ketone into rats resulted in the irreversible binding of radioactivity to liver proteins. When the rats were pretreated with phenobarbital, this binding was increased and extended to proteins of some other tissues and to DNA and RNA of liver and DNA of kidney. (Author abstract) (13 Refs)

56. ENTEROHEPATIC FATE OF AFLATOXIN B1 (MEETING ABSTRACT).

Wong JJ, Kayashima L, Hsieh PH
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):33 1981

Previous metabolic research on the potent food-borne carcinogen, aflatoxin B1 (AFB1) has primarily focused upon the liver and only speculated upon its interrelationship with the gastrointestinal tract in AFB1 disposition and toxicity. Using in situ metabolism techniques, male Sprague-Dawley rats received intestinal doses of 14C-AFB1 equivalent to that calculated for 24 hr dietary exposure to 1ppm AFB1. Curve-fit estimates of AFB1 absorption indicates that the total hepatic exposure to AFB1 would equal approx 5 ug or 27% of dose within 24 hr. Intraportal injection of less than 4 ug of AFB1 indicates that excretion in the bile begins within 10 min. Estimates indicate that within 24 hr approx 64% of dose would be excreted in the bile. High pressure liquid chromatography and thin layer chromatography analysis of the bile failed to detect AFB1 or any of its known metabolites. Preliminary Ames mutagen tests have not detected any bile-borne mutagenic activity. Venous blood sampled from the inferior vena cava revealed a concentration of less than 1.0% of dose/ml blood. Approx 40% of this amount was bound to blood proteins, 30% associated with aqueous phase, and no 'free' AFB1 detected. Re-injection of bile into the small intestine did not result in detectable reabsorption. Evidence indicates that during chronic dietary exposure to AFB1, the liver is capable of substantial first-pass extraction and efficient biliary elimination of AFB1 metabolites. Biliary-borne metabolites appear to represent detoxification products and not subject to enterohepatic recirculation. (no Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

57. HEPATOCELLULAR CARCINOMA AND HEPATITIS-B-VIRUS: MORE ON THEIR RELATIONSHIP (MEETING ABSTRACT).

de Franchis R, Primignani M, Vecchi M, Zannier PM, Colombo M, Colucci G, Tommasini M
Clinica Medica III, University of Milano, Milan, Italy
Gastroenterology; 80(5,part2):1329 1981

To evaluate the strength of the association of Hepatocellular Carcinoma (HCC) with current or past Hepatitis-B-Virus (HBV) infection, serum HBV markers were studied in three groups of age and sex-matched patients: (a) 33 subjects with HCC, b) 33 patients with chronic active hepatitis and c) 33 hospitalized controls. Sera were tested for hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc, anti-HBc titre, HBeAg and anti-HBe by radioimmunoassay by means of commercially available kits (Abbott). The overall exposure rate to HBV (positivity for any one marker) was 94% in HCC, 85% in CAH, and 57% in controls. The prevalence of HBsAg was 36%, 12% and 9% in the three groups respectively. Prevalence of anti-HBs was much lower in HCC (3%) than in CAH (48%) and in controls (39%). Conversely, the prevalence of isolated anti-HBc positivity was 54% in HCC, 24% in CAH and 9% in controls. Serologic evidence of current HBV infection (HBsAg positivity, high-titre anti-HBc or HBeAg positivity) was more common in HCC (54%) than in CAH (18%) and controls (9%). The overall exposure rate to HBV is similar in HCC and CAH. However, serological evidence of continuing viral replication is much more common in the former group. A defective clearance of HB V in HCC is a possible explanation of the phenomenon. (no Refs)

58. OCCURENCE OF HEPATOMA IN PATIENTS WITH B-TYPE OR NON-B TYPE LIVER CIRRHOSIS (MEETING ABSTRACT).

Motoike Y, Kuma S, Okuda H, Fujino N, Takeda K, Sujino H, Hashimoto E, Saito A, Obata H
Gastrointestinal Diseases Center, Tokyo Women's Medical Sch., Shinjuku-ku, Tokyo 162, Japan
Proceedings of the 17th Annual Meeting of Japan Society of Hepatology held in Gifu, Japan, 25-26 June, 1981. Japan Society of Hepatology, Tokyo 113, Japan, 148 pp., 1981.

The patients examined were 35 whose av age was 46 yr and who were diagnosed as being continuously infected with hepatitis B virus (HBV) and showed anti HBc greater than or equal to 210 (immune adherence hemagglutination method) (B group) and 44 whose av was 53 yr and who were not infected with HBV and did not show anti HBc (non-B group). They were examined for at least 6 mo. The occurrence of hepatoma was determined by periodically measuring alpha-fetoprotein (AFP) and by ultrasonic methods. Hepatoma occurred in nine (7 males) of the patients in the B group and eight (7 males) of the patients in the non-B group. The av age of the patients who contracted hepatoma was 56 yr and 60 yr for the B and non-B groups, respectively. Hepatoma occurred in one and four of the patients who had a previous history of hepatitis in the B and non-B groups, and in eight and four of the patients in the same groups, respectively, who did not have such a history. Of the patients in the B and non-B groups who contracted hepatoma, zero and one patient, respectively, had a previous history of transfusion, but nine and seven patients did not. One patient each in the B and non-B groups was a heavy drinker. The av time from the beginning of the survey to the occurrence of hepatoma for the B group was 2 yr and 11 mo, and that for the non-B group was 5 yr and 1 mo. More than half of the patients in the B group had fluctuating GOT values before the occurrence of hepatoma while seven of the patients in the non-B group had stable values. The AFP value rapidly increased from the normal range in six of the group B patients and gradually increased from the maintained abnormal value in five of the non-B group patients. Two of the non-B group patients showed no AFP production. The e antigen-antibody system for most of the patients in the B group fluctuated without any accompanying seroconversion, but one patient had seroconversion about 3 mo before the definite diagnosis for occurrence of hepatoma. (no Refs) (In JPN)

59. PREVALENCE OF HEPATITIS B SURFACE ANTIGEN (HBSAG) AND ANTIBODY (ANTIHBS) IN PRIMARY LIVER CANCER DETERMINED BY RADIOIMMUNOASSAY AND PASSIVE HEMAGGLUTINATION TECHNIQUES (MEETING ABSTRACT).

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No affiliation given
Eur J Nucl Med; 6:A23 1981

In previous studies from Senegal, HBsAg was found by agar gel diffusion or counterelectrophoresis techniques in serum of 39-42% of patients with primary liver cancer (PLC) as compared to 9-11% of controls. We report herein an investigation of the prevalence of HBsAg and antiHBs, utilizing in comparative trial the most sensitive of current assay methods. The study related to 164 subjects of black race from West Africa living in Senegal: 82 PLC matched with 82 age/sex hospitalized controls. HBsAg was determined by the Ausria II 125 test and antiHBs by the Ausab system: two solid phase radioimmunoassay procedures. The sera were also tested by passive hemagglutination assay (PHA). The serologic manifestations of HB are usual for PLC in Senegal. For each group the HBsAg and antiHBs frequencies were significantly higher with radioimmunoassay (RIA) than with PHA. The most important difference is registered for the controls. So, in order to value the prevalence RIA was the most sensitive procedure. Consequently, in PLC 71% against 17% in the controls very high level of contamination with the Australian antigen was observed a low immune response to surface antigen of the HB virus: presence of antibodies in 22% of the cases only among the PLC against 58% for the controls. This pattern found of the surface indicators in PLC fits in most cases with the unfavorable evolution of chronic hepatitis: persistance of HBsAg and no appearance of antiHBs antibodies. (2 Refs)

60. LIVER CELL DYSPLASIA IN ASSOCIATION WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS AND HEPATITIS B SURFACE ANTIGEN IN HONG KONG.

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Int J Cancer: 28(5):571-574 1981

Liver-cell dysplasia was identified in 60% of 558 cases of cirrhosis with and without hepatocellular carcinoma (HCC) in Chinese coming to necropsy in Hong Kong from 1963 to 1978. A significant correlation was found between liver-cell dysplasia and the identification of hepatitis B surface antigen (HBsAg) in the livers, suggesting that dysplasia may be causally related to hepatitis B virus (HBV). Applying Bayes' theorem to our series of male deaths, we calculated that for Chinese male non-cirrhotics showing liver-cell dysplasia at necropsy, compared with male non-cirrhotics showing no liver-cell dysplasia, the approximate risk factor for HCC is 13:1, whereas for male cirrhotics with liver-cell dysplasia, compared with male cirrhotics without liver cell dysplasia, the risk factor for HCC is approx 2:1. In the presence of dysplasia, the risk for HCC is increased two-fold in males who are also HBsAg-positive. Thus, the presence of liver-cell dysplasia in cirrhotic or non-cirrhotic livers accompanies a significantly higher risk of developing HCC, especially in the presence of HBsAg. (Author abstract) (10 Refs)

61. INTEGRATION OF HEPATITIS B VIRUS DNA INTO THE GENOME OF LIVER CELLS IN CHRONIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA. STUDIES IN PERCUTANEOUS LIVER BIOPSIES AND POST-MORTEM TISSUE SPECIMENS.

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N Engl J Med; 305(18):1067-1073 1981

Recombinant-DNA technology combined with gel electrophoresis was used to find hepatitis B virus DNA (HBV-DNA) in liver and tumor tissue from patients with hepatocellular carcinoma and chronic liver disease, and to study integration of HBV-DNA into the genome of the tissue cells. HBV-DNA analysis was performed on hepatocellular carcinomas from 20 patients, all of whom had at least one serological marker indicating intercurrent or previous HBV infection. Twelve patients whose sera were positive for hepatitis B surface antigen (HBsAg) had integrated HBV-DNA in the tumor; 3/8 who were HBsAg negative but positive for antibody to HBsAg (anti-HBs) also had HBV-DNA integration. Five patients who were HBsAg negative but anti-HBs positive had no detectable HBV-DNA in their tumors. In some patients integrated HBV-DNA was also found in nontumorous liver tissue with the same or different hybridization pattern from that of tumor. In five HBsAg carriers with evidence of the carrier state and chronic liver disease for less than 2 yr, HBV-DNA was present but not integrated in liver tissue. In two patients who carried HBsAg for greater than 8 yr, HBV-DNA was integrated into the host genome. The studies suggest that integration of HBV-DNA into hepatocytes occurs during the course of persistent hepatitis B virus infection and precedes development of gross neoplasm. (22 Refs)

62. GAMMA-GLUTAMYL TRANSFERASE IN HUMAN HEPATOMA COMPARED WITH ADULT AND FETAL LIVER ENZYMES (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:51 1981

The aim is to elucidate and compare some of enzymic and immunological properties of gamma-glutamyl transferase (gamma GT) of hepatoma tissues with those of adult and fetal liver enzymes. Gamma-GT was solubilized from human hepatoma or other tissues and partially purified by chromatography on diethylaminoethanol-cellulose and Sephadex G-200 column. An electrophoretic study showed that hepatoma gamma-GT had a slightly slower mobility than that of the other two enzymes, independently of neuraminidase treatment. Fetal liver gamma-GT had a similar mobility to adult liver enzyme. Hepatoma gamma-GT was distinguished from the other two enzymes by decreased affinity to Concanavalin A (Con A) sepharose. However, hepatoma enzyme was found to be very similar to normal adult liver enzyme in terms of mol wt, Michaelis constant, pH optimum, thermostability, effect of various L-amino acids as acceptors, behavior to divalent cations or ethylene-diaminetetraacetate, and inhibition by urea or sodium dodecyl sulfate. Furthermore, analysis by Ouchterlony double diffusion technique revealed the enzymes from the three sources shared the same antigenic site. These results suggest that the hepatoma gamma-GT seems to occur possibly by the altered glycosilation of the glycoprotein having similar peptide bonds. (no Refs)

63. SEX DIFFERENCE IN THE ACQUISITION OF GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) POSITIVE FOCI IN THE LIVER OF SPRAGUE-DAWLEY RATS FED POLYCHLORINATED BIPHENYLS (PCB) (MEETING ABSTRACT).

Cihla HP, Weltman RH, Pitot HC, Norback DH
Department of Pathology, Middleton Memorial Veterans Hospital, Madison, WI
Toxicologist; 1(1):137 1981

The potential of a PCB mixture (Aroclar 1260) or a pure congener, 2,3,6,2',3',6',-hexachlorinated biphenyl (HCB), to induce gamma glutamyl transpeptidase positive hyperplastic foci and hepatocellular carcinoma (HCC) was studied. Serial liver sections (obtained at 9, 12 and 15 mo from male and female rats fed diets containing Aroclor 1260 [100 ppm from 13 mo followed by 50 ppm], HCB [100 ppm for 9 mo followed by intermittant exposure at 50 ppm] or control feed) were histochemically assayed for GGT activity and histologically assessed. No enzymatic or histopathic alteration was noted with HCB feeding. Progressive change was induced with Aroclor-1260 feeding and is described. At 9 mo, both male and female rat liver showed centrilobular hypertrophy that was not associated with GGT activity. Only females developed hyperplastic foci that were homogenously GGT positive (MD equals 133 um, mean diameter of the enzyme-altered foci). Males showed a higher number of diffuse, GGT-positive areas (MD equals 79 um). All controls were negative. At 12 mo, females showed an increase in number and size of GGT foci (MD equals 245 um) and female controls yielded a background incidence of GGT-positive areas (MD equals 73 um). By 15 mo, both sexes yielded hyperplastic foci with homogeneous GGT activity, while females showed progression to neoplastic nodules and HCC heterogeneous for GGT activity (female control MD equals 44 um, female experimental MD equals 1157 um). No fibrotic changes were noted. (no Refs)

64. SURVEY OF SPONTANEOUS AND CARCINOGEN-INDUCED RODENT TUMORS FOR GAMMA FETAL ANTIGEN (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:47 1981

Previous studies revealed the presence of a 35,000 dalton gamma-migrating antigen in saline extracts of several mouse fibrosarcomas and hepatic carcinomas. This antigen was designated gamma-fetal antigen (gamma-FA) since it possessed gamma electrophoretic mobility and could be extracted from late-gestation mouse fetuses. To determine the extent to which gamma-FA is associated with spontaneous and carcinogen-induced murine cancers, neoplasms representing 12 different tissue sites of origin were examined serologically. Gamma-FA was identified in 17 of 23 such tumors with malignancies of neural ectoderm generally constituting the gamma-FA-negative class. Mice bearing gamma-FA-positive tumors had detectable levels of gamma-FA in their sera. Immunochemical and physico-chemical analysis of gamma-FA extracted from several histologically distinct tumor types indicated that the antigen detected in each case was indeed gamma-FA. The occurrence of gamma-FA in 75% of the malignant tumors examined, its presence in the sera of mice bearing transplanted and primary cancers and the absence of this antigen in the serum of normal mice suggests an associative relationship of potential diagnostic value. This possibility is supported by the observation that immunoprecipitable gamma-FA appeared in the sera of hepatocarcinogen-treated rats several wk prior to the initial detection of alpha-fetoprotein. (no Refs)

65. CHANGE IN HEPATIC GLUTATHIONE (GSH) LEVELS IN MALE AND FEMALE F344 RATS TREATED WITH LOW PROTEIN AND DIETARY AFLATOXIN (AFB1) (MEETING ABSTRACT).

Mainigi KD, Campbell TC
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Toxicologist; 1(1):130 1981

It has been proposed that the level of hepatic GSH may play an important role in determining the proportion of procarcinogenic aflatoxin dose that eventually binds to critical cellular macromolecules. The primary objectives of this study were to investigate the effects of different levels of protein intake and ingestion of hepatotoxic doses of AFB1 on both, hepatic GSH levels and the induction of hepatic lesions. After acclimation to a 20% casein (20C) agar-gel diet for 6 days, groups of weanling male (71g) and female (76g) rats were fed 5C or 20C diets with/without 2.5-5 ppm AFB1 for 6 wk. Animals were sacrificed at selected intervals during this time period and liver GSH concentrations were determined. After the first 12 hr, rats were always killed between 9 and 10 AM to minimize diurnal variations in GSH level. In terms of growth rate, females were quite resistant, both to protein deficiency and dietary AFB1. Males were considerably more responsive to both treatments. On the other hand, the GSH levels in both sexes showed similar response patterns to dietary stresses. All rats on 5C showed decreased levels of GSH, beginning within 3 hr of this treatment. AFB1 increased GSH level regardless of protein status and animal sex. Whereas bile duct proliferation was seen in all AFB1-treated liver, regenerating nodules appeared only in 20C-AFB1 rats. Lesions were more acute in males, but in both sexes they were more pronounced in 20C groups. (no Refs)

66. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

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Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

67. ANALYSIS OF THE SUGAR CHAINS OF HUMAN ALPHA-FETOPROTEIN (AFP) USING LECTIN AFFINITY (MEETING ABSTRACT).

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Proceedings of the 17th Annual Meeting of Japan Society of Hepatology held in Gifu, Japan, 25-26 June, 1981. Japan Society of Hepatology, Tokyo 113, Japan, 148 pp., 1981.

The sugar chains of the AFP in the serum of 15 patients with hepatocellular carcinoma and 3 with metastatic hepatoma were examined in comparison with those in the umbilical cord blood of 7 individuals, and with those in the serum of 1 patient with a yolk sac tumor. Concanavalin A (Con A) and lens bean lectin (LcH) which have an affinity for mannose and glucose were used as the lectins. The affinity of AFP for lectin was measured by the cross immunoaffino-electrophoresis method (Bphi-Hansen's method). The AFP was separated into two subfractions, one binding and the other not binding to Con A. The percentages of the nonbinding subfraction in the AFP of the umbilical cord blood, the serum of the patients with hepatocellular carcinoma and of the serum of the patients with metastatic hepatoma or yolk sac tumors was 0%, 5-10%, and 45-60%, respectively. The affinity of AFP for LcH was divided into three groups, nonLcH-binding, loosely LcH-binding and tightly LcH-binding. There was only a negligible amount of LcH-binding AFP fraction in all the diseases, and the ratio of the nonbinding to the highly binding fraction in the AFP produced by the various diseases showed no specific tendency. On the other hand, this ratio in the umbilical cord blood was relatively constant, the nonbinding fraction accounting for 80-100%. In conclusion, AFP showed microheterogeneity with regard to affinity for lectin. The affinity for Con A of the AFP produced by metastatic hepatoma was totally different from that of the

AFP produced by hepatocellular carcinoma, and resembled that produced by the yolk sac tumor. Therefore, it was thought that AFP could be used to distinguish AFP-producing hepatocellular carcinoma from AFP-producing metastatic hepatoma. (no Refs) (In JPN)

68. GUINEA-PIG AFP DURING NORMAL ONTOGENESIS, LIVER CARCINOGENESIS, AND UNDER HORMONE TREATMENTS (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:P6 1981

Guinea-pig alpha fetoprotein (AFP) was purified to homogeneity, characterized, and a radioimmunoassay was developed. Serum AFP level in fetal guinea-pig remains in the mg/ml range up to the 8th gestational wk and then drops rapidly. The electrophoretic and lectin affinity molecular variants of AFP change during ontogenesis, probably in relation with changes in carbohydrate composition of the protein. The liver and the yolk sac are the main sites of AFP synthesis during fetal life with the stomach and the small intestine contributing smaller amounts, as measured by peptide pulse labeling assays in vivo. Compared to other species, serum AFP levels are very high in normal adult guinea-pig; these levels are reduced dramatically by administration of glucocorticoids or ACTH. The hormone effect is rapidly reversed upon withdrawal. In guinea-pigs fed with diethylnitrosamine, serum AFP increases at the time liver tumors appear; there is no early induction and the increase is much less than in rats under similar treatment. (no Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

69. QUANTITATIVE STUDIES OF EARLY STAGES IN MOUSE HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Goldfarb S, Pugh TD, Koen H, Vesselinovitch SD
University of Wisconsin, Madison, WI
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We previously reported that single ip injections of diethylnitrosamine (5 ug per g body wt) in 15-day-old male B6C3 F1 mice caused the early induction of foci of RNA-rich hepatocytes that lacked glucose-6-phosphatase activity, showed high rates of cell replication, and had a strong tendency to invade terminal hepatic veins. The foci showed features of tumor progression including a doubling of tritiated thymidine labeling indices between 20 to 28 wk and the development at 44 wk into typical trabecular hepatocellular carcinomas. Recently, we carried out serial section reconstructions of over 700 foci in a total of 17 livers from mice killed at 10, 20 and 28 wk. Foci were assigned to one of nine different log incremental size classes with equatorial plane areas between .005 to 2.5 mm2. The av number of foci per liver was 313 at 10 wk, 938 at 20 wk, and 1,050 at 28 wk. Because the foci were close to spherical in shape and increased in number, we believe that regression or remodeling did not occur. Despite a slowing down in the rate of emergence of the foci, their aggregate tumor vol continued to increase logarithmically through 36 wk of study. A method using smoothing splines and developed in collaboration with statisticians at the University of Wisconsin accurately estimated the number and size distribution of foci. The unequivocal identification of malignant and premalignant lesions in solid organs and the accurate quantitation of their number, size, and growth rates, should greatly facilitate the determination of potency of initiators and promoters of carcinogenesis. (1 Ref)

70. SEQUENTIAL, LIGHT AND ELECTRON MICROSCOPIC ANALYSIS OF HEPATOCELLULAR CARCINOMA INDUCED BY AROCLOR 1260 (MEETING ABSTRACT).

Weltman RH, Norback DH
William S. Middleton Memorial Veterans' Hospital and University of, Wisconsin Madison, WI
Toxicologist; 1(1):65 1981

Progressive hypertrophic (HT), hyperplastic (HP) and neoplastic (N) growth was observed in female Sprague-Dawley rats continuously exposed to a diet containing 100 ppm, followed by 50 ppm, Aroclor 1260. The liver of control rats showed no gross, lobular or subcellular changes. Central cell hypertrophy was present following 1 mo of Aroclor exposure. The eosinophilic HT cell contained increased smooth endoplasmic reticulum (ER), cytoplasmic vacuoles (CV), lipid droplets (LD) and a hyperchromatic nucleus with a large nucleolus. Foci and areas of HP cells were observed in all livers following 9 mo of Aroclor exposure. In addition to HT cell cytoplasmic characteristics, HP cells possessed increased nuclear chromatin granules, LD and pseudo inclusions. Scanning electron microscopy (SEM) of HP cells revealed disordered cellular arrangement and dilated, tortuous canalicular channels. Firm, elevated, tan, 0.5-1 cm N growths were observed in all livers examined after 15 mo of Aroclor exposure. Four-cell-thick trabeculae, acinar arrangements, hemorrhage, necrosis and a few mitoses indicate that the large N growths are hepatocellular carcinoma. In addition to the cellular features of HP cells, N cells contained nucleolar segregation, concentric membrane arrays, short stacks and single strands of rough ER, and abundant mono- and polyribosomes. Rough ER encircled mitochondria and peroxisomes. In pericanalicular regions microvilli-lined CV and abundant filaments were observed. SEM of N tissue showed disordered cellular arrangement, dendritic canalicular channels and many surface particles. (no Refs)

71. QUANTITATION OF DIFFERENCES BETWEEN SPONTANEOUS AND INDUCED LIVER TUMORS IN MICE WITH AN AUTOMATED IMAGE ANALYZER.

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Lab. Experimental Pathology, NCI, Frederick Cancer Res. Center, Building 560, Room 32-93, Frederick, MD, 21701
Cancer Lett; 14(2):143-150 1981

Morphologic differences between spontaneous hepatocellular neoplasms of B6C3F1 mice and those induced with Nitrofen were investigated using an image analyzing computer. Groups of 50 male and 50 female mice were fed diets containing 2,348 or 4,696 ppm Nitrofen for 78 wk. Histologic examination of liver tumors in control mice revealed two patterns: (1) those composed primarily of a uniform population of basophilic hepatocytes, usually smaller than normal hepatocytes (hepatocellular adenoma) and (2) those with larger cells arranged in prominent trabeculae (hepatocellular carcinoma). Tumors in mice fed Nitrofen were composed of hepatocytes larger than normal hepatocytes, with abundant eosinophilic cytoplasm forming solid patterns. Basophilic neoplasms were distinguished from control liver tissue, as were eosinophilic hepatocellular neoplasms induced by Nitrofen. Furthermore, these tumors could be distinguished from one another. The observations indicate that quantitative morphologic differences exist between the spontaneous and induced neoplasms. It is concluded that Nitrofen acts as a true carcinogen, not a promoting agent. (18 Refs)

72. CHEMICAL LIVER CARCINOGENESIS, MONITORING OF THE PROCESS BY FLOW CYTOMETRIC DNA-MEASUREMENTS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The carcinogenic process in the liver was monitored from early non-neoplastic changes to the development of tumors in two well known models; giving Dimethylnitrosamine (DMN) ip to newborn mice, and feeding rats with Acetylaminofluorene (AAF). Liver parenchyma cells and liver tumor cells were isolated by collagenase treatment and prepared for flow cytometric (FCM) measurements of nuclear DNA content. The changes observed were correlated to morphology and 3H-thymidine incorporation. The early preneoplastic changes in hepatocytes from DMN-treated mice were shifts in the DNA content to classes of higher nuclear ploidies. AAF-feeding of rats caused gradual distortion of the DNA content of nuclei from parenchymal cells. After 16 wk of exposure, before any tumors were seen, a majority of the nuclei displayed an aneuploid DNA content. The significance of these changes in the carcinogenic process is discussed, and a possible use of these models for detection of hepatotrophic agents and agents causing aneuploidy (clastogens and turbagens) is proposed. The liver neoplasias (adenomas and hepatocellular carcinomas) induced by these models contained tumor stemlines with diploid DNA content, some hepatocellular carcinomas showed aneuploidy. Proliferative nodules contained diploid and tetraploid stemlines. (no Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

73. POTENCY OF AFLATOXIN B1 AND AFLATOXIN M1 IN CYTOTOXICITY AND DNA REPAIR ASSAYS (MEETING ABSTRACT).

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Toxicologist; 1(1):42 1981

Although the acute toxicity and carcinogenicity of aflatoxin B1 (AFB1) has been thoroughly documented, relatively little is known of the potency of aflatoxin M1 (AFM1), a hydroxylated metabolite of AFB1. Therefore, the cytotoxicity and genotoxicity of AFB1 and AFM1 were compared using in vitro system of primary cultures of rat hepatocytes. Hepatocytes were cultured for 20 hr (2.5 x 10(6) cells/dish) in hormone supplemented culture medium. The incubation was continued for an additional 24 hr with the test chemicals and 0.5 uCi/ml [3H] thymidine ([3H]TdR). Cytotoxicity was assessed by measuring lactate dehydrogenase released into the culture medium. Both AFB1 and AFM1 were potent cytotoxins. LDH levels were elevated significantly above controls for AFB1 at 0.1 ug/dish and for AFM1 at 0.6 ug/dish. However, LDH concentrations rose to the same max of approx 200% of controls for AFB1 and AFM1 at a dose of 1.2 ug/dish. Genotoxicity was assessed by measuring unscheduled DNA synthesis by two different methods, incorporation of [3H] TdR into trypsin-resistant acid-precipitable material and autoradiographic analysis. AFB1 and AFM1 were both positive and about equally potent in the DNA repair assay using either technique. In vivo experients indicate a higher level of DNA binding for AFb1 than AFM1. There are two plausible explanations for the DNA repair data; 1) AFB1 and AFM1 bind to DNA to approx the same extent in the hepatocyte culture system, 2) less AFM1 is covalently bound to DNA than AFB1 but AFM1 adducts are more efficiently repaired. (1 Ref)

74. CHARACTERIZATION OF DNA REPAIR ELICITED BY CARCINOGENS AND DRUGS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

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J Toxicol Environ Health; 8(3):463-477 1981

Autoradiographic unscheduled DNA synthesis measured in the hepatocyte primary culture/DNA repair test after exposure to chemical carcinogens was characterized. Replicated and nonreplicated hepatocyte DNA was separated by CsCl gradient centrifugation. Uptake of 3H-thymidine into nonreplicated DNA was seen after exposure of hepatocytes to the activation-independent carcinogen methyl methanesulfonate or the activation-dependent carcinogen N-2-acetylaminofluorene, but not with fluorene, a noncarcinogen. N-4-acetylaminofluorene, a mutagen with uncertain carcinogenicity, also elicited DNA repair. Density gradient centrifugation allowed the detection of DNA repair in hepatocytes following exposure to the antihistamines pyrilamine maleate and tripelennamine HCl. Methapyrilene did not elicit repair. (44 Refs)

75. CHARACTERIZATION OF THE HEPATIC DNA DAMAGE CAUSED BY 1,2-DIBROMOETHANE USING THE ALKALINE ELUTION TECHNIQUE.

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Carcinogenesis; 2(9):839-844 1981

Hepatic lesions induced by 1,2-dibromoethane (EDB: 25-75 mg/kg, ip) in male Swiss Webster mice were assessed by a modified alkaline elution assay. The major changes were use of 47-mm diameter filters and a microfluorometric technique to quantify the DNA. EDB administration caused a dose-dependent increase in DNA strand breaks. Allowing the DNA sample to remain on the filter in the presence of pH 12.3 buffer facilitated the conversion of alkali-labile sites to strand breaks detectable by the alkaline elution technique. To determine the presence of DNA cross-linking after EBD exposure, one-half of the hepatic nuclei were x-irradiated (200 rads) at 0 C. No EBD-induced DNA-DNA or DNA-protein cross-links were detected. This method may be useful for studying the nature of DNA damage induced by in vivo carcinogens. (22 Refs)

76. DNA METHYLATION AND METHYLASE LEVELS IN NORMAL AND MALIGNANT MOUSE HEPATIC TISSUES.

Lapeyre JN, Walker MS, Becker FF
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Carcinogenesis; 2(9):873-878 1981

DNA methylation levels (expressed as the percentage of 5-methylcytosine relative to total cytosines) were measured in normal mouse liver, primary hepatocellular carcinomas (PHCs) in male C3H mice, PHCs induced in male C7Bl/6N mice by chlordane, N-acetylaminofluorene, or 3'methyl-4-dimethylaminoazobenzene, and spontaneous and chemically induced PHCs in male (C7BL/6H x C3H/HeN)F1 (B6C3) mice. All tumors demonstrated an undermethylation of their genomes, compared with normal livers of age-matched controls. The undermethylation was not due to inactivation of or deficiency in DNA methylase activity, since enzyme levels in tumor nuclei were higher than background levels. The possibility that aberrations in DNA meth ylation are involved in the transformation of normal differentiated cells to neoplastic cells is discussed. (57 Refs)

77. INHIBITION OF RAT LIVER AMINOACYL-TRNA SYNTHETASES IN VITRO AFTER ACUTE AND CHRONIC AFLATOXIN B1 ADMINISTRATION IN VIVO.

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Chem Biol Interact; 37(1):233-244 1981

In a cell-free system the influence of acute aflatoxin B1 administration on the fractions of the hepatic microsomal translation complex of female rats was examined and compared with the influence of chronic aflatoxin B1 treatment. Polypeptide synthesis determined by [14C]leucine incorporation with a postmitochondrial supernatant was inhibited by 80% 24 hr after acute aflatoxin B1 administration whereas inhibition was only 17% in animals 30 wk after chronic treatment. After acute aflatoxin B1 administration inhibition of protein synthesis was by 67%, mainly on the polysomal level, whereas inhibition with the pH 5 enzyme was only by 22%. After chronic aflatoxin B1 administration inhibition was by 18%, mainly with the pH 5 enzyme and by only 6% on the polysomes. The inhibition by pH 5 enzyme was further investigated with regard to aminoacyl-tRNA synthetases, components of pH 5 enzyme. Leucine-specific aminoacyl-tRNA synthesis was inhibited by 20% 24 hr after acute and by 12% 30 wk after chronic aflatoxin B1 treatment. Aminoacyl-tRNA synthetase activities in a crude synthetase preparation tested with five amino acids were found to be noncompetitively inhibited. It is concluded that the inhibition of protein synthesis after acute and chronic aflatoxin B1 administration is in part due to decreased aminoacyl-tRNA levels caused by inhibited aminoacyl-tRNA synthetases. (Author abstract) (39 Refs)

78. INCREASED ACTIVITY OF A NEUTRAL PROTEASE IN CYTOSOL FROM RAT HEPATOMA INDUCED BY N-2-FLUORENYLACETAMIDE.

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(c/o Tsukada) Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Cancer Res; 41(12):5130-5133 1981

A protease active with N-alpha-benzoyl-DL-arginine-p-nitroanilide with an optimum pH of 7.3 has been found in the cytosol of rat liver. The activity of this protease increased in N-2-fluorenylacetamide-induced hepatoma as well as in fetal liver. It has been purified from normal liver and hepatoma about 200-fold. Its mol wt is estimated by gel filtration to be about 200,000 in each tissue. The protease activity is unaffected by chymostatin, pepstatin, soybean trypsin inhibitor, and p-chloromercuribenzoate. Antipain, leupeptin, tosyl-L-lysine chloromethyl ketone, and phenylmethylsulfonyl fluoride inhibit the protease activity. This protease appears to be a serine protease. (Author abstract) (22 Refs)

79. AN INCREASE IN CALMODULIN DURING GROWTH OF NORMAL AND CANCEROUS LIVER IN VIVO.

MacManus JP, Braceland BM, Rixon RH, Whitfield JF, Morris HP
Animal/Cell Physiology Group, Natl. Res. Council Canada, Ottawa K1A OR6, Canada
FEBS Lett; 133(1):99-102 1981

Change in the calcium receptor protein, calmodulin (CaM), during growth of normal liver and a greater content of CaM in solid liver tumors is reported. Specific pathogen free liver as well as Morris hepatomas were utilized. Tissues were excised, homogenized and total, soluble, and particulate samples prepared. Radioimmunoassay for CaM was performed using 125I labeled CaM, 2 ug anti-CaM, and standard amounts of CaM or tissue extracts. CaM content was also measured by stimulation of a cyclic-nucleotide phosphodiesterase (PDE). Results show no change in CaM content of liver after sham hepatectomy. CaM content in the soluble fraction of liver increased three fold after 68% partial hepatectomy, returning to normal after 18 hr. No change was observed in the particulate fraction of regenerating liver. Assay of CaM dependent cyclic nucleotide PDE confirmed increase of CaM during liver regeneration. The increase of CaM during liver regeneration coincides with the time when calcium is required for DNA synthesis. The relevance of the CaM rise to the calcium dependence has yet to be established. Fetal or neonatal liver had the same CaM concentration as adult liver. Various liver tumors contained more CaM than normal adult or fetal liver. The increase in CaM content in virally transformed cells in vitro is apparently a characteristic of the neoplastic state. The evidence of CaM increase during regeneration possibly indicates that CaM may be involved with the control of cell proliferation. (23 Refs)

80. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER: A NEW TUMOR MODEL (MEETING ABSTRACT).

Li SA, Li JJ
Medical Research Laboratories, Veterans Administration Center, Minneapolis, MN, 55417
Fifth International Symposium of the Journal of Steroid Biochemistry, July 13-15, 1981, Puerta Vallarta, Jalisco, Mexico. Journal of Steroid Biochemistry 80 pp., 1981.

A definite causal relationship exists between estrogens and liver tumors in women. At present there are no adequate estrogen inducible experimental liver tumor models available. The spontaneous liver tumor incidence in Syrian golden hamsters is negligible and the incidence of hepatomas following continuous diethylstilbestrol (DES) or other estrogens, as in other rodents, has been reported to be low. Our present results indicate at least a 60% incidence in multifoci liver neoplasms in castrate male hamsters treated with DES for 8.0-mo and fed a diet containing 0.2% alpha-naphthoflavone (alpha-NF); an inhibitor of mixed function oxygenases. There is a nearly 3-fold elevation in specific estrogen binding in the livers of animals treated with

DES for 2-to 3-mo compared to untreated hamsters and at least a 6-fold increase in liver estrogen receptor in hamsters treated with DES + alpha-NF. Sucrose gradient centrifugation analyses indicate either 8S or 8S + 4S binders in liver cytosols derived from these animals based on competition at 100-fold excess radioinert DES concentrations. Enhanced retention of estrogen receptor complex was observed in purified nuclei derived from hamsters treated with DES + alpha-NF compared to untreated controls. These findings may have an important role in liver tumorigenesis in the hamster. (no Refs)

81. 3,5,3'-TRIIODOTHYRONINE(T3) AND 3,3'5',-TRIIODOTHYRONINE (REVERSE T3;RT3) SYNTHESIS IN TUMOR-BEARING ANIMALS (MEETING ABSTRACT).

Ong M, Malkin DG, Malkin A
Department of Clinical Biochemistry, Sunnybrook Medical Centre, Toronto, Canada
Oncodev Biol Med; AbstractsBook,1:52 1981

Since the synthesis of rT3 appears to be a characteristic feature of fetal ontogeny, we undertook to determine whether a reversion from T3 to rT3 synthesis would take place in experimental animal tumors and, in addition, whether hepatic and renal deiodination of T4 would show a similar reversion in these tumor-bearing animals. We chose as animal models the R3230AC mammary tumor grown in Fischer 344 rats and two variants of the Morris 5123 hepatoma, the 1-1 and 81-B, grown in Buffalo rats. Tumor, hepatic and renal tissues were analyzed for 5-and 5'-deiodinase activity using standard techniques. The following results were obtained: (1) in the Fischer 344 rats, the mammary tumor was found to contain both 5-and 5'-deiodinase activities (normal lactating mammary glands contain no detectable enzyme activity), (2) compared to normal controls, hepatic and renal T3 synthesis increased significantly while rT3 synthesis remained unaltered in the mammary tumor-bearing rats, (3) in the hepatoma-bearing rats, the hepatomas contained 5- and 5'-deiodinase activity comparable to those present in the liver, (4) both T3 and rT3 synthesis were significantly less than normal in the liver of the hepatoma-bearing rats, (5) renal synthesis of T3 and rT3 in both normal and all tumor-bearing rats was significantly greater than hepatic synthesis of these hormones. We conclude that: (1) significant differences in the behavior of 5-and 5'-deiodinase occur in different tumor models, (2) there is no evidence of retro-differentiation of 5-deiodinase activity either within the tumor or at remote sites in these particular animal models. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

82. HEPATOCELLULAR CARCINOMA IN 1981.

Sherman M, Terblanche J, Kirsch RE
UCT-MRC Liver Res. Group, Dept. Medicine, Univ. Cape Town Medical Sch., Observatory, Cape, South Africa
S Afr Cancer Bull; 25(1/2):31-33 1981

Incidence, course, diagnosis, and treatment of hepatocellular carcinoma (HCC) in South Africa are discussed. HCC shows definite geographic and racial variation in incidence, is identifiable by the presence of alpha-fetoprotein (AFP), and may present different clinical courses. Factors related to development of HCC include aflatoxin and hepatitis B virus (HBV). In South Africa HBV infection occurs at an early age in rural Blacks, possibly explaining why these patients develop HCC as early as the third decade. Patients with hemochromatosis and cirrhosis also have an increased risk of HCC. In South African Blacks, HCC is a fulminant rapidly fatal disease. Peak age of onset is the third and fourth decades as compared with the fifth and sixth decades elsewhere. Few South African Blacks survive greater than 1 yr from the time of diagnosis; death is usually due to the tumor rather than underlying liver disease. AFP levels greater than 1,000 nanog/ml are usually diagnostic of HCC. AFP is elevated in greater than 95% of South African Black patients and levels greater than 1,000 nanog/ml are found in greater than 60%. Several invasive and non-invasive methods for detection of this tumor are described. The only certain curative therapy is resection of the affected lobe when the underlying liver is normal and the tumor is confined to a single lobe. In most South African patients, this is very unusual and most HCC are inoperable. Among Coloreds, resectability is higher, but still low. Liver transplants have been performed for HCC, but many patients have died from metastases. Chemotherapy or radiotherapy for African HCC is of little value. (4 Refs)

83. STRUCTURALLY DIVERSE HEPATOCARCINOGENS IN VITRO INDUCE DRUG RESISTANCE IN RAT HEPATOCYTES WHEN TESTED IN VITRO (MEETING ABSTRACT).

Carr BI
Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, 91010
Br J Cancer; 43(5):731 1981

Carcinogen-altered cells have generally been shown to be more resistant to the toxic effects of carcinogens than normal cells. It was therefore reasoned that the marked resistance of human hepatocellular carcinoma to cytotoxic chemotherapy might also be due to a carcinogen-induced phenotypic change in hepatocytes, resulting in an increased resistance to both carcinogen- and chemotherapy-mediated cytotoxicity. Male F344 rats were fed a basal diet and given aflatoxin B1 (AFB1) 30 ug daily ip or a basal diet containing either ethionine or 3'-methyl-4-dimethylaminoazobenzene. Rats were sacrificed weekly and their hepatocytes were placed in primary monolayer culture. Following a 3 hr attachment hepatocytes were exposed for 24 hr to Adriamycin (1.8x10-4M) cycloheximide (7x10-3M) or AFB1 (10-6M). Resistance was defined as the percentage of attached cells excluding trypan blue compared to untreated controls. Each of the 3 carcinogens induced greater than 50% resistance to AFB1 in the isolated hepatocytes after one wk, and comparable resistance to cycloheximide and Adriamycin after 4 wk. Hepatocytes from normal rats did not survive these concentrations of test drugs. In vivo, 3 different hepatocarcinogens induced marked resistance in rat hepatocytes to the potent carcinogen AFB1, as well as to the cytotoxic drug Adriamycin, using an in vitro assay, several mo before the appearance of hepatocellular carcinoma. Clinical drug resistance may be an early carcinogen-induced phenotype in primary tumors. (3 Refs)

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1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. EPIDEMIOLOGY OF CANCER IN CHILDHOOD.

Li FP, Bader JL
Sidney Farber Cancer Center, Boston, MA
Hematology of Infancy and Childhood Volume II. Nathan DG and Oski FA, ed. Philadelphia, W. B. Saunders Company, 774 pp., 1981.

The incidence of malignant neoplasms in children less than 15 yr old in the United States is discussed. Of 7,168 new cases reported in 1970, leukemia was the most frequently occurring cancer (2,357) followed by tumors of the CNS (1417), lymphoma (787), neuroblastoma (540), soft tissue sarcoma (463), Wilms' tumor (450), bone tumor (323), retinoblastoma (197), liver tumor (100), ovarian tumor (77), testicular tumor (57), and others (400). Cancer risk factors discussed are the environmental carcinogens ionizing radiation, drugs, chemicals, and infectious agents. Host susceptibility includes single-gene diseases, chromosomal disorders, familial cancers, and cancer and birth defects. (288 Refs)

2. POWER CONSIDERATIONS IN EPIDEMIOLOGIC STUDIES OF VINYL CHLORIDE WORKERS.

Beaumont JJ, Breslow NE
Industrywide Studies Branch F-8, Natl. Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Am J Epidemiol; 114(5):725-734 1981

Nine retrospective mortality studies of workers exposed to vinyl chloride were reviewed to determine whether differences in their hypothesis testing results might be due to differences in statistical power. Where possible, the power of each study was calculated for cancer of the lung, brain and liver. When power was taken into consideration, the results for liver and brain cancer were found to be consistent with an etiologic role for vinyl chloride. For lung cancer, the data were not consistent with an etiologic role, in that two studies with very high power yielded negative results. (Author abstract) (16 Refs)

3. RETHINKING THE ENVIRONMENTAL CAUSATION OF HUMAN CANCER.

Higginson J
International Agency Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
Food Cosmet Toxicol; 19(5):539-548 1981

Epidemiologic studies concerning the etiology of environmental cancers are reviewed. The results of a number of studies strongly suggest that most human cancers are related to environmental factors and not to racial or hereditary factors. The results of the author's survey in South Africa further suggested that 'way of life' was of major significance for many cancers, especially those of the gastrointestinal tract and endocrine-dependent organs. Although there are many factors involved in its etiology, cancer may be prevented by controlling a single predominant factor. Only a small part of the total cancer burden can be directly related to ambient environmental pollution, and a number of other environmental factors, particularly diet, must be considered for the majority of environmental cancers. Although the role of dietary factors in promotion and enzyme induction of cancers is well established in laboratory animals, their role in man is much less clear. Most epidemiologists do not consider human environmental cancers in terms of single causes; human cancers for which there is evidence of multistage and multifactorial origin include lung, esophagus, liver, stomach and large intestine, breast and endometrium, Burkitt's lymphoma, and nasopharyngeal carcinoma. (106 Refs)

4. HOW HIGH A PERCENTAGE OF ENVIRONMENTALLY RELATED CANCER CASES CAN BE PREVENTED IN NORWAY?.

Langard S
Yrkesmedisinsk avdeling, Telemark sentralsjukehus, 3900 Porsgrunn, Norway
Tidsskr Nor Laegeforen; 101(28):1602-1606 1981

Approx 110,000 cases of cancer were recorded in Norway during the period 1966-1975. Esophageal cancer was diagnosed in 1.099 cases, gastric cancer in 11,702, cancer of the gastrointestinal tract in 9,270, rectal cancer in 4,670, cancer of the liver and bile ducts in 253, pancreatic cancer in 3,992, larynx cancer in 745, lung cancer in 7,608, prostate cancer in 10,835, renal cancer in 3,191, cancer of the bladder and urinary tract in 4,047, and malignant lymphoma in 3,336. The percentage of environmentally related, ie, preventable cancer was estimated after extrapolation to the 1979 incidence. According to the low estimate, 2,250 cases of cancer were attributable to smoking, 300 to alcohol consumption, and 150 to occupational exposure. (15 Refs) (In NOR)

5. ORAL CONTRACEPTION AND CANCER RISK.

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Schweiz Med Wochenschr; 111(46):1742-1748 1981

Oral contraception was introduced 20 yr ago and is today the most popular method of preventing pregnancy. Some undesirable side effects of these drugs are well known, while others are only suspected. Many investigations have been undertaken to elucidate whether or not the Pill has carcinogenic properties, and the present study describes the current state of knowledge on this question. At present no evidence exists to suggest that oral contraceptives have carcinogenic effects on the human breast or genital organs. A causal relationship between use of these drugs and development of liver tumors is possible but far from proven. (Author abstract) (39 Refs) (In GER)

TUMOR INDUCTION IN ANIMALS

6. DOSE RESPONSES OF FIVE HEPATOCARCINOGENS FOR THE INITIATION OF RAT HEPATOCARCINOGENESIS.

Imaida K, Shirai T, Tatematsu M, Takano T, Ito N
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Cancer Lett; 14(3):279-283 1981

Dose response curves were generated for hepatocarcinogenesis in male Fischer 344 rats initiated by diethylnitrosamine (DEN), aflatoxin-B1 (AFB), N-2-fluorenylacetamide (FAA), 3'-methyl-4-dimethylaminobenzene (DAB), or dimethylnitrosamine (DMN). Two wk after initiation, animals were placed on a 0.02% FAA diet for 2 wk. Animals were partially hepatectomized (PH) at the end of wk 3 and killed at the end of wk 4. All five hepatocarcinogens exhibited clear dose response curves for initiation of hepatocarcinogenesis;

both numbers and areas of hyperplastic nodules increased with increasing doses in all cases. AFB was the most potent initiator, and was effective at a dose as low as 0.25 mg/kg body wt. Sizes of no dules induced by DEN, FAA, and DMN were smaller than those induced by AFB and DAB. (12 Refs)

7. PROLIFERATION OF PRENEOPLASTIC LESIONS AFTER DISCONTINUATION OF CHRONIC DEN FEEDING IN THE DEVELOPMENT OF HEPATOMAS IN RAT.

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Laboratoire d'Anatomie Pathologique, Universite de Liege au Sart Tilman, Tour de Pathologie, 4000 Liege, Belgium
Br J Cancer; 44(4):561-566 1981

The compound diethylnitrosamine (DEN, 10 mg/kg/day) was fed to rats for 2, 4, and 6 wk. At different times after feeding with DEN was stopped, growth preneoplastic lesions has been correlated with pathological evolution (preneoplastic foci, neoplastic nodules and hepatomas). The proliferating fraction in the foci, the cell content, and relative vol of foci increase as a function of the duration of the treatment. The proliferating fraction increases evenly throughout the liver, but, in all experimental modalities, preneoplastic cells show a proliferative advantage over the phenotypically normal tissue. In each experimental group, the proliferative rate correlates with the pathological evolution. After 2 wk of DEN feeding the growth activity of foci remains very low, and neoplastic nodules are not detectable until the median time of death (14 mo). After 4 and 6 wk, a critical size of the foci is reached, corresponding to the neoplastic transformation, and an increased labeling index is triggered in the lesions and in the phenotypically normal tissue. It is speculated that the 'growth pressure' induced by the first carcinogen treatment, associated with the subsequent disturbance of the mitotic control regulation, may be implicated in the process of malignant transformation of preneoplastic lesions. (Author abstract) (13 Refs)

8. THE EFFECT OF 4-SUBSTITUTION ON THE CARCINOGENICITY OF NITROSOPIPERIDINE.

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Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Carcinogenesis; 2(10):1045-1048 1981

Nitrosopiperidine (NPIP), 4-phenylnitrosopiperidine, 4-cyclohexylnitrosopiperidine, and 4-tertiary-butylnitrosopiperidine were administered at equimolar (0.88) concentrations in drinking water, 5 days/wk, to groups of 20 female Fishcher 344 rats, for 50-60 wk. Like NPIP, both 4-phenyl- and 4-tertiary-butyl-NPIP induced esophageal papillomas and carcinomas in almost all animals, although time to death with tumors was considerably longer with the phenyl compound and still longer with the tertiary-butyl compound. Forestomach carcinomas occurred in 2/20 animals treated with 4-tertiary-butyl NPIP but in none of the animals treated with the other three compounds. Only 4-phenyl-NPIP induced liver tumor, 7 angiosarcomas and 14 hepatocellular carcinomas. Tongue papillomas (5) or carcinomas (7) occurred only in rats treated with 4-tertiary-butyl-NPIP. In general, NPIP induced tumors more quickly after admini stration of a smaller total dose than the other three compounds. The results indicate that all three derivatives of NPIP are considerably less carcinogenic than NPIP itself and that the 4-cyclo-hexyl derivative had no carcinogenic activity at the dose studied. The fact that only the 4-phenyl derivative induced liver tumors may be related to formation of phenolic compounds. (11 Refs)

9. LACK OF CARCINOGENICITY IN MICE OF 4,4'-DIAMINOBENZANILIDE AND 4,4'-DIAMINOAZOBENZENE, TWO INTERMEDIATES USED IN THE MANUFACTURE OF AZO DYES.

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Cancer Lett; 14(3):329-336 1981

A long-term bioassay for carcinogenicity of 4,4'-diaminobenzanilide (DABA) and 4,4'-diaminoazobenzene (DAAB) was conducted in BALB/c mice. Male and female mice received DABA or DAAB in the diet (100, 300, or 600 ppm) beginning at 8 wk of age and continuing for 60 wk. Animals were then returned to a normal diet and observed for an additional 80 wk. No differences were seen between any of the treated groups and controls. No association was observed between treatment and incidence of any particular tumor with the exception of adrenal cortex tumors, which were seen at lower incidence in DAAB-treated males. Malignant lymphomas originated most frequently in the spleen, mesenteric lymph nodes, and Peyer's patches, and were seen more frequently in females but not in excess of control values. Liver cell tumors occurred with very low frequency. (15 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

10. INHIBITION OF DENA-LIVER CARCINOGENESIS IN RATS WITH SODIUM OXYFERRISCORBONE.

Blagoeva PM, Balanski RM
Oncological Res. Inst., Medical Acad., Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(5):711-712 1981

Hepatocarcinogenesis induced in male BD/6 rats by nine weekly ip injections of diethylnitrosamine (80 mg/kg body wt) was reduced by 33% when animals were treated with a prophylactic regimen of sodium oxyferriscorbone (2 mg/kg body wt, ip five times per wk for 5 mo). It is suggested that sodium oxyferriscorbone may interfere with the oxidation-reduction processes in target tissues. (12 Refs)

11. INHIBITORY EFFECT OF 4,4'-DIAMINODIPHENYLMETHANE ON LIVER, KIDNEY AND BLADDER CARCINOGENESIS IN RATS INGESTING N-ETHYL-N-HYDROXYETHYLNITROSAMINE OR N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE.

Fukushima S, Hirose M, Hagiwara A, Hasegawa R, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(10):1033-1037 1981

Effects of 4,4'-diaminodiphenylmethane (DDPM) in the 'post-initiation' stage of liver, kidney, and bladder carcinogenesis induced in male F344 rats by N-ethyl-N-hydroxyethylnitrosamine (EHEN) or by N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were investigated. Rats given 0.1% E HEN in drinking water for 2 wk followed by DDPM treatment (0.1% in diet, 32 wk) had significantly fewer renal neoplastic nodules (av 0.28/square cm [cm2]) and renal cell tumors (av 0.16/cm2) than rats treated with EHEN alone (1.88 neoplastic nodules and 0.51 renal cell tumors/cm2). DDPM did not inhibit development of hyperplastic nodules in the liver. However, hepatocellular carcinomas did not occur in rats treated with EHEN and DDPM, whereas they were observed in 7/21 rats treated with EHEN alone. DDPM (0.1% in diet, 34 wk) also reduced the frequency of bladder papillomas induced by 4 wk or BBN treatment (0.01% in drinking water). In these experiments, rats treated with DDPM showed growth retardation and decreased food intake. (25 Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

12. MODULATION OF THE COVALENT BINDING OF ARYL HYDROCARBON METABOLITES TO DNA IN VITRO AFTER TREATMENT OF RATS AND MICE WITH TRANS-STILBENE OXIDE.

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Carcinogenesis; 2(10):1049-1056 1981

Effects of trans-stilbene oxide (TSO) on in vitro microsome-mediated binding of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) to purified DNA were investigated. Chromatograms of enzyme digests of DNA obtained from incubation of labeled BP metabolites with hepatic microsomes from TSO-treated Sprague-Dawley rats showed a decrease in peak H (nucleoside-bound 9-hydroxy-BP-4,5-oxide) without any significant modification of peaks E (nucleoside-bound syn- and anti-BP-7,8-diol-9,10-epoxide) or G (nucleoside-bound BP-4,5-oxide). In vitro addition of the epoxide hydrolase inhibitor 1,1,1-trichloropropene 2,3-oxide (TCPO) produced 2.8-and 3.2-fold increases, respectively, in peaks G and H in microsomes from TSO-treated rats compared with those from controls. BP-metabolite-deoxyribonucleoside profiles obtained with microsomes from rats treated with BP (40 mg/kg) alone showed considerable covalent binding of BP-7,8-diol-9,10-epoxide and 9-hydroxy-BP-4,5-oxide; treatment with both BP and TSO (3 x 400 mg/kg) decreased binding to 45% and 25%, respectively. Microsomes from TSO-treated Swiss mice showed levels of BP-4,5-oxide and 9-hydroxy-BP-4,5-oxide binding that were 1.6-and 1.4-fold, respectively, greater than levels in microsomes from controls. The heights of peaks E, G, and H for C57BL/6 mice treated with TSO and BP were 53%, 60%, and 69% of the values obtained for mice treated with BP alone. After incubation of DNA with 3H-DMBA and BP- or TSO plus BP-treated rat liver microsomes, dual induction by BP and TSO was found to decrease DMBA metabolite binding to DNA, compared with induction by BP alone. The studies demonstrated the ability of TSO to increase the rate of oxidation at the K-region, due to induction of specific monooxygenases, and its ability to increase the rate of deactivation of epoxide intermediates by inducing microsomal epoxide hydrolase activity. The effects of TSO were similar for both substrates examined. (29 Refs)

13. TUMORIGENICITY OF BAY-REGION DIOL-EPOXIDES AND OTHER BENZO-RING DERIVATIVES OF DIBENZO(A,H)PYRENE AND DIBENZO(A,I)PYRENE ON MOUSE SKIN AND IN NEWBORN MICE.

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Cancer Res; 42(1):25-29 1982

Dibenzo(a,h)pyrene [DB(a,h)P], dibenzo(a,i)pyrene [DB(a,i)P], and seven of their benzo-ring derivatives were tested for tumorigenic activity on mouse skin and in newborn mice. In the tumor studies on mouse skin, a single topical application of 50, 200, or 600 nmol of compound was followed 7 days later by twice-weekly applications of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate for 16 or 24 wk. With the exception of 2,10-difluorodibenzo(a,i)pyrene, all of the compounds had significant tumor-initiating activity at all doses tested. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene, the metabolic precursors of bay-region diol-epoxides, had tumor-initiating activity that was equivalent to their parent hydrocarbons. Saturation of the double bond in the benzo-ring of these dihydrodiols resulted in the formation of tetrahydrodiols whose tumor-initiating activity was not significantly different from that observed with the corresponding dihydrodiols at the 50-nmol dose. The bay-region diol-epoxides of DB(a,h)P and DB(a,i)P, in which the benzylic hydroxyl group and the oxirane oxygen are trans (Isomer 2), induced significantly fewer tumors per mouse than did their dihydrodiol and parent hydrocarbon precursors. In the tumorigenicity study in newborn mice, a total dose of 87.5 nmol of the hydrocarbon divided into three ip injections was administered on the 1st, 8th, and 15th day of life, and tumorigenic activity was determined when the mice were 49 to 54 wk old. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene induced three- to eight-fold more pulmonary tumors per mouse and four- to five-fold more hepatic tumors per male mouse than the respective parent hydrocarbons. The corresponding tetrahydrodiols had no more than one-eighth of the pulmonary tumorigenic activity of the corresponding dihydrodiol. The bay-region diol-epoxide (Isomer 2) of DB(a,h)P had tumorigenic activity equal to the parent hydrocarbon but significantly less than its dihydrodiol precursor. The bay-region diol-epoxide (Isomer2) of DB(a,i)P was highly toxic, and only 19% of the mice survived to termination of the study. This diol-epoxide had significantly less tumorigenic activity towards the lung than did either its dihydrodiol precursor or the parent hydrocarbon. Notably, 20% of the surviving mice treated with the diol-epoxide of DB(a,i)P had leukemia at the termination of the study. 2,10-Difluorodibenzo(a,i)pyrene had no tumorigenic activity in newborn mice at the single dose tested. These results are discussed in relationship to the bay-region theory of polycyclic aromatic hydrocarbon carcinogenicity. (Author abstract) (27 Refs)

14. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Sci Tech Aerosp Rep; 19(18):2533 1981

An environmental carcinogen, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diolepoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

15. THE ACTIVATION OF AFLATOXIN B1 IN LIVER SLICES AND IN BACTERIAL MUTAGENICITY ASSAYS USING LIVERS FROM DIFFERENT SPECIES INCLUDING MAN.

Booth SC, Bosenberg H, Garner RC, Hertzog PJ, Norpoth K
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Carcinogenesis; 2(10):1063-1068 1981

Activation of aflatoxin B1 (AFB1) was compared in two in vitro systems: binding to DNA in liver slices incubated with 14C- or 3H-AFB1 and in standard bacterial mutation systems using 9000 x gravity supernatant (S-9) fractions from uninduced livers for activation. The results were compared in several rodent species in an effort to correlate them with known trends in carcinogenicity. Covalent binding of 14C-AFB1 to DNA from liver slices showed the order rat greater than hamster greater than mouse. Phenobarbitone pretreatment of rats decreased binding, and binding of aflatoxin G1 (AFG1) was less than that of AFB1. These findings all were correlated with relative susceptibility to AFB1-induced hepatocarcinogenesis. An exception to this trend was the similar level of binding found in male and female rat livers. Levels of 3H-AFB1 binding to DNA in human liver biopsies ranged from 0.7-8.5 nanog AFB1/mg DNA, which was similar to the range seen in the mouse and hamster. Mutagenicity data did not correlate with carcinogenicity in relation to species differences, as the efficiencies of livers from the three species for activating AFB1 mutagenicity were hamster greater than rat greater than mouse. AFG1 mutagenicity generally was markedly less than that of AFB1 when activated by rat liver S-9. The correlation between AFB1 binding to DNA in liver slices in various rodent species and susceptibility to AFB1 hepatocarcinogenesis and its modification in the rat by phenobarbitone suggests that these differences are related to differences in metabolic activation of AFB1 to its reactive species, its subsequent detoxification, and macromolecular interaction. (30 Refs)

16. METABOLIC ACTIVATION OF AFLATOXIN B1 BY LIVER TISSUE FROM MALE FISCHER F344 RATS OF VARIOUS AGES.

Jayaraj A, Richardson A
Dept. Biological Sciences, Illinois State Univ., Normal, IL, 61761
Mech Ageing Dev; 17(2):163-171 1981

The effect of aging on the ability of the liver to activate chemical procarcinogens was studied using 12-, 18-, and 27-mo-old male Fischer F344 rats. The cytochrome P-450 content of the S9 and microsomal fractions of the liver decreased approx 30% between 12 and 18 mo of age. The structural conformation of cytochrome P-450 in microsomes from 12-, 18-, and 27-mo-old rats was studied using electron-spin resonance spectroscopy. An age-related decrease in the amount of cytochrome P-450 ferric iron in the liver microsomes was observed. The conversion of the chemical procarcinogen aflatoxin B1 to mutagenic compounds by the S9 and microsomal fractions of liver was measured using the Salmonella typhimurium bioassay. A 40-50% decrease in the metabolic activation of aflatoxin B1 was observed between 12 and 18 mo of age. However, the activation of aflatoxin B1 did not change after 18 mo of age. The age-related decrease in the activation of aflatoxin B1 by liver appears to be due to a decrease in the metabolic activity of the mixed-function oxidase system. (Author abstract) (27 Refs)

17. COMPARISON OF THE IN VITRO METABOLISM OF N-NITROSOHEXAMETHYLENEIMINE BY RAT LIVER AND LUNG MICROSOMAL FRACTIONS.

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Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):59-64 1982

The in vitro metabolism of N-nitrosohexamethyleneimine by lung and liver microsomes and cytosol from uninduced male Fischer rats is described. Metabolites produced by both organs appeared to be identical. The liver subcellular fractions had a lower Km (0.6 mM) than did lung fractions (3 mM) and metabolized 2.5 to 5x as much nitrosamine per mg protein. Our results, together with those from our earlier studies, indicate that, as the size of the carbon ring increases from nitrosopyrrolidine to nitrosohexamethyleneimine lung microsomes had an increased affinity for the cyclic nitrosamines; there was only a small effect with liver enzymes. This suggests that microsomal enzymes that metabolize cyclic nitrosamines in rat livers and lungs are not the same. The first stable alpha-hydroxylation product, 6-hydroxyhexanal, was not detected in reactions involving microsomes alone. Apparently, this compound is rapidly converted to 1,6-hexanediol by liver or lung microsomes. The presence of cytosol was needed for the full conversion of these metabolites to epsilon-hydroxycaproate and max alpha-hydroxylation activity. Epsilon-Aminocaproate was always found in direct proportion to the hydroxyacid, suggesting that both acids arise from the same alpha-hydroxylation event by different breakdown mechanisms. Beta- and gamma-hydroxynitrosohexamethyleneimine were not metabolized significantly by rat liver enzymes and thus, in this species, may be 'detoxification products' of N-nitrosohexamethyleneimine. (Author abstract) (20 Refs)

18. EXCESSIVE ACCUMULATION OF AUTOFLUORESCENT LIPOFUSCIN IN THE LIVER DURING HEPATOCARCINOGENESIS BY METHYL CLOFENAPATE AND OTHER HYPOLIPIDEMIC PEROXISOME PROLIFERATORS.

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Cancer Res; 42(1):259-266 1982

Several hypolipidemic drugs and certain industrial plasticizers induce proliferation of peroxisomes and enhance the activities of peroxisome-associated enzymes in the livers of rodents. Evidence now suggests that potent hepatic peroxisome proliferators as a class are carcinogenic, although they do not appear to be mutagenic in the Salmonella-microsome assay system. We now report that long-term administration of methyl-2-[4-(p-chlorophenyl)phenoxy]-2 methylpropionate, a potent hepatic peroxisome proliferator, at a dietary concentration of 0.1% (w/w), induced hepatocellular carcinomas in 14 of 14 male F344 rats between 65 and 75 wk. The tumor cells contained several peroxisomes. Consistent with this observation was the finding of increased levels of carnitine acetyltransferase, heat-labile peroxisomal enoyl coenzyme hydratase, and peroxisomal beta-oxidation system in the tumors. As expected, methyl clofenapate was not mutagenic in the Salmonella-microsome assay using Salmonella typhimurium strains TA98 and TA100. Abundant accumulation of autofluorescent lipofuscin in the nontumorous portions of liver in rats bearing methyl-2-[4-(p-chlorophenyl)phenoxy]-2-methylpropionate induced hepatocellular carcinomas was observed. The examination in this study of livers of rats bearing hepatocellular carcinomas induced previously by five other hypolipidemic peroxisome proliferators provided retrospective evidence for increased accumulation of autofluorescent pigment in the liver cells. It is suggested that accumulation of lipofuscin in the livers of rats fed peroxisome proliferators serves as evidence for the increased production of biologically damaging free radicals as a result of H2O2 generated by sustained proliferation of peroxisomes. The hypothesis that persistent proliferation of peroxisomes and increase in peroxisomal beta-oxidation system initiates the neoplastic transformation of liver cells by increasing the intracellular production of DNA-damaging H2O2 and other reactive oxygen intermediates (OH-, O2-, 1O2) remains to be tested. (Author abstract) (49 Refs)

19. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

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Food Cosmet Toxicol; 19(5):657-666 1981

This review of safrole metabolism is aimed at elucidating the importance of the allyl moiety and the methylenedioxy group in the mechanism of carcinogenesis. It includes studies concerning safrole carcinogenicity, interactions of safrole with cytochrome P-450, inhibition of mixed-function oxidase activity by safrole, ligand complex formation with cytochromes P-450 and P-448, and hemoprotein formation by safrole and isosafrole. Ligand complexing and covalent binding of reactive intermediates with the heme and protein moieties, respectively, of cytochrome P-450, may be fundamental to the mechanism of safrole carcinogenesis. Structural and functional properties of the cytochrome are substantially changed by this binding, which, since ribosomes are attached to the endoplasmic reticulum at cytochrome P-450, may be associated with loss of ribosomes known to occur following treatment with safrole or other carcinogens. Chemical carcinogenesis is associated with increases in hepatic cytochrome P-448 and simultaneous loss of cytochrome P-450 activity and could, through loss of ribosomes, result in impairment of glycoprotein synthesis and thus contribute to malignant transformation by epigenetic mechanism. Therefore, of the two functional groups of safrole, the allyl group has been shown to be associated with mutagenicity, and the methylenedioxy moiety to be associated with changes to cytochrome P-450 and possibly with epigenetic aspects of carcinogenicity. (84 Refs)

20. METABOLIC ACTIVATION OF A TRYPTOPHAN PYROLYSIS PRODUCT, 3-AMINO-1-METHYL-5H-PYRIDO(4,3-B)INDOLE (TRP-P-2) BY ISOLATED RAT LIVER NUCLEI.

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Cancer Lett; 14(3):261-266 1981

The abilities of nuclei and microsomes to convert 3-amino-1-methyl-5H-pyrido[3,4-b]indole (Trp-P-2) to an active mutagen were compared. Nuclei from polychlorinated biphenyl or methylcholanthrene-treated rats activated Trp-P-2 and caused a greater number of revertants in the Salmonella mutation test than nuclei isolated from phenobarbitol-treated or non-treated rats. Similar pretreatment effects were observed with microsomal activation. (17 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

21. LIVER CELL MEMBRANE ALLOANTIGENS AS CELLULAR MARKERS IN GENOTYPIC MOSAIC RAT LIVERS UNDERGOING CHEMICALLY INDUCED HEPATOCARCINOGENESIS.

Hunt JM, Buckley MT, Onnink PA, Rolfe PB, Laishes BA
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Cancer Res; 42(1):227-236 1982

We have developed a new marker system utilizing rat alloantigens as genetic cellular markers for hepatocytes in genotypic mosaic livers of rats undergoing hepatocarcinogenesis. This marker system has been designed to facilitate the eventual purification of subpopulations of hepatocytes from such livers which contain precursor cells of carcinomas. Thus, a lineage relationship between cells of early putative premalignant liver lesions and those of carcinomas may ultimately be established, and the process of cancer development may be biochemically probed. A donor-to-host liver cell transplantation procedure was used. Host rats subjected to a 2-acetylaminofluorene/partial hepatectomy regimen were grafted orthotopically iv with donor liver cells via a mesenteric vein of the hepatic portal system. Cryostat sections of host rat livers were prepared 10 to 13 days after donor liver cell transplantation for histochemical localization of gamma-glutamyltranspeptidase-positive (GT+) hepatocyte colonies Genotypic mosaic host rat livers were further analyzed by indirect immunofluorescence in serial cryostat sections to identify hepatocyte colonies on the basis of their strain-specific alloantigens. Polyvalent F344 anti-WF alloantiserum was prepared by immunizing F344 rats with WF skin and spleen cells. The resulting serum reacted positively by indirect immunofluorescence with cryostat liver sections as well as collagenase-dissociated hepatocytes from WF and WF x F344F1 hybrid rats. No reaction of the alloantiserum with F344 liver tissue or isolated hepatocytes was observed. Some F344 donor origin colonies did not express the GT+ phenotype and were classified as gamma-glutamyltranspeptidase-negative. With the aid of tissue architectural landmarks, 276 individual colonies were analyzed. Ninety-seven per cent of the colonies appeared to be of F344 donor origin (92% FA- GT+; 5% FA- gamma-glutamyltranspeptidase-negative); 3% were FA+ GT+; and apparently of F1 hybrid host origin. Rat alloantigens expressed on the surface of hepatocytes may offer the potential for purification of donor-origin putative premalignant hepatocytes from genotypic mosaic host rat livers at sequential stages of hepatocarcinogenesis. (31 Refs)

22. AN IMMUNOHISTOCHEMICAL STUDY ON THE LOCALIZATION AND DISTRIBUTION OF EPOXIDE HYDROLASE WITHIN LIVERS OF UNTREATED RATS.

Kawabata TT, Guengerich FP, Baron J
(c/o Baron) Dept. Pharmacology, Coll. Medicine, Toxicology Center, Univ. Iowa, Iowa City, Iowa, 52242
Mol Pharmacol; 20(3):709-714 1981

Antiserum produced against epoxide hydrolase (EH) which had been purified to apparent homogeneity from rat hepatic microsomes was used in qualitative and semiquantitative immunohistochemical procedures to examine in greater detail the localization and distribution of EH within livers of untreated male and female mice. The immunohistochemical staining produced using the unlabeled antibody peroxidase-antiperoxidase technic was specific for EH. In sections prepared from the median lobes of livers from untreated male rats, staining for EH was evident in hepatocytes throughout the liver but not in cells associated with the hepatic vasculature, Kupffer cells, and sinusoidal cells. Significant regional differences in EH concentration were observed within the liver lobule. The staining was of a fine, particulate nature and was uniformly dispersed throughout the cytoplasms of hepatocytes. Marked differences in the intracellular distributions of EH and various forms of cytochrome P-450 within hepatocytes in livers of untreated male rats were indicated. These differences may be of great importance during the metabolic activation and inactivation of mutagens, carcinogens, and other xenobiotics in liver. The EH activity of the hepatocyte nucleus seem to be predominantly associated with the nuclear envelope. Similar EH distributions were observed in the livers of other untreated male and female rats. Fluorescent immunohistochemical studies showed similar EH distributions. The data suggested that hepatocytes lying within the midzonal and periportal regions of the lobule contain significantly less enzyme than do centrilobular hepatocytes. Thus centrilobular hepatocytes may possess the greatest capacity to generate reactive and toxic electrophilic epoxide metabolites from xenobiotics and to inactivate these epoxides by hydration to form trans-dihydrodiols. (27 Refs)

23. LOCALIZATION AND MORPHOLOGICAL OBSERVATION OF ENZYME-LABELLED IMMUNOFETOPROTEIN IN HUMAN LIVER CANCER AND PERICANCEROUS LIVER TISSUE.

He D, Dai Y, Tao W, Wang H, Wu g, Ping B, Zheng B
Dept. Pathologic Anatomy, Second Military Medical Coll., People's Republic of China
Zhonghua Yixue Jianyan Zazhi; 4(1):12-16 1981

In recent yr, the distribution of alpha-fetoprotein (AFP) in liver cancer and its relationship to hepatocarcinogenesis has been reported. However, the distribution of AFP in pericancerous liver tissue in primary hepatoma patients has not been reported. Results of AFP distribution studies are described for 22 cases of primary hepatoma (17 males, 5 females), using an indirect enzyme-labeled antibody technic. Surgical liver specimens were used. It was found that AFP was distributed mainly in the cytoplasm of cancer and pericancerous cells. The distribution was mostly diffused, with only a small portion localized in a particular part of the cytoplasm, beneath the cell membrane or around the nucleus. Tissue distribution of AFP was random, with most AFP-positive cells located at the edge of the cancer mass, in the lobule and around intrahepatic veins. In most cases, AFP-positive rate was higher in pericancerous cells than in liver cancer cells and was related to the activity of chronic liver diseases. (15 Refs) (In CHI)

24. CLUSTERING OF HEPATITIS B VIRUS INFECTION AND HEPATOCELLULAR CARCINOMA IN A FAMILY.

Gilmore IT, Harrison JM, Parkins RA
Royal Liverpool Hosp., Liverpool L7 8XP, England
J R Soc Med; 74(11):843-845 1981

Family clustering of primary hepatocellular carcinoma (HCC) is well recognized, although rare. One possible reason for such clustering has become apparent since the advent of tests to detect circulating markers of hepatitis B virus infection, and this has been the common etiological factor in three families studied. We report the results of screening a Chinese family following the death of one member who had been found to have HCC associated with hepatitis B surface antigenemia. Four of seven siblings were traced: one had died of HCC 5 yr earlier, and evidence of past or present hepatitis B infection was found in the remaining three, one of whom was also found to have HCC. (Author abstract) (24 Refs)

25. HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS. A PROSPECTIVE STUDY OF 22,707 MEN IN TAIWAN.

Beasley RP, Lin CC, Hwang LY, Chien CS
Univ. Washington Medical Res. Unit, 15-2 Kung Yuan Road, Taipei, Taiwan
Lancet; 2(8256):1129-1133 1981

A prospective general population study of 22,707 Chinese men in Taiwan has shown that the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis B surface antigen (HBsAg) is much higher than among non-carriers (1,158/100,000 vs 5/100,000 during 75,000 man-yr of follow-up). The relative risk is 223. PHC and cirrhosis accounted for 54.3% of the 105 deaths among HBsAg carriers but accounted for only 1.5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the etiology of PHC. (Author abstract) (25 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

26. CYTOCHEMICAL AND BIOCHEMICAL MICROANALYSIS OF CARCINOGENESIS.

Bannasch P, Benner U, Hacker HJ, Klimek F, Mayer D, Moore M, Zerban H
Abteilung fur Cytopathologie, Institut fur Experimentelle Pathologie, Deutsches Krebforschungszentrum, D-6900 Heidelberg 1, W. Germany
Histochem J; 13(5):799-820 1981

The use of analytical cytochemistry, enzyme cytochemistry, autoradiography, microdissection, and biochemical microanalysis in the elucidation of mechanisms of cell transformation is reviewed. The first cytopathologic phenomenon which can be detected by cytochemical means during the process of hepatocarcinogenesis is an excessive storage of glycogen. Hepatocellular glycogenesis is related to the dose and time of carcinogen treatment and to the development of hepatocellular tumors. A sequence of cellular changes has been established leading from the glycogen-rich hepatocyte, which appears clear or acidic in hematoxylin/eosin sections, to the basophilic hepatoma cell, which is poor in glycogen but rich in ribosomes. Excessive storage of polysaccharides or lipids is correlated with the development of other tumors as well, including renal epitheliomas induced in rats by oral application of nitrosomorpholine. Three types of epithelial kidney tumors develop under these conditions, all with specific histogenesis and cytogenesis. Extensive light-, electron- and fluorescent micrographs illustrate the text. (68 Refs)

27. DISTRIBUTION OF NUCLEAR SIZE AND DNA CONTENT IN SERIAL LIVER BIOPSIES OF RATS TREATED WITH N-NITROSOMORPHOLINE, PHENOBARBITAL AND BUTYLATED HYDROXYTOLUENE.

Romagna F, Zbinden G
Inst. Toxicology, Swiss Federal Inst. Technology, Univ. Zurich, Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland
Exp Cell Biol; 49(6):294-305 1981

Nuclear size distribution and DNA content distribution were determined in liver biopsies of rats using an electronic particle counter and an impulse cytophotometer, respectively. Nuclear size distribution and DNA content distribution were found to be highly correlated regardless whether peak areas or peak heights of the histograms were compared. Treatment with the hepatocarcinogen N-Nitrosomorpholine (NNM) caused a dose-dependent increase in octoploid nuclei and a shift of the 2 n:4 n ratio in favor of the diploid nuclei. Treatment with Pb and BHT had minor effects on nuclear size and DNA content distribution. The paper demonstrates the usefulness of fine-needle aspiration biopsy procedure for the evaluation of liver changes induced by chemical substances. (Author abstract) (13 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

28. TISSUE-DEPENDENT ENZYME-MEDIATED REPAIR OR REMOVAL OF O-ETHYL PYRIMIDINES AND ETHYL PURINES IN CARCINOGEN-TREATED RATS.

Singer B, Spengler S, Bodell WJ
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Carcinogenesis; 2(10):1069-1073 1981

Ten-day-old BD IX rats were injected with radiolabeled N-ethyl-N-nitrosourea (EtNU: 69.4 ug/kg, ip), and the sites and proportions of ethyl products, as well as their removal and repair, in DNA from various tissues was examined. One hr after carcinogen injection, DNA of brain, liver, and other pooled organs (spleen, lung, thymus, muscle, and intestine) showed similar proportions of the derivatives quantitated (O6-ethyl [Et] guanine [G], 7EtG, 3-Et adenine [A], O2-Et thymine [T], O4-EtT, O2-Et cytosine [C], and ethylphosphotriesters). During the 75 hr after carcinogen administration, most ethylated bases were poorly removed (or, in the case of O4-EtT, not at all) from DNA in the brain (the target tissue of EtNU carcinogenicity), and from DNA in the tissue pool. Removal from the brain appeared to cease after 25-50 hr. Kinetics of O6-EtG removal in brain and in the tissue pool were similar, except that there was a rapidly exhausted early and partial repair capability in brain. O-alkyl products were removed from the liver at progressively increasing rates over the entire 75-hr period. The accelerated loss of O2-EtT, O4-EtT, and O2-EtC may have been due either to an increase in hepatic protein synthesis as a result of recovery from EtNU-induced inhibition or to induction of an O-alkyl pyrimidine-specific enzyme. Triester levels remained almost unchanged in all tissues examined. However, the small decrease in the triester level observed in liver DNA suggested a half-life of greater than 1 wk. Any or all persistent promutagenic derivatives (O6-EtG, O2-EtT, O4-EtT, O2-EtC) may be important in initiation of carcinogenesis by somatic mutation. (45 Refs)

29. EFFECT OF 1,2-DIMETHYLHYDRAZINE AND DIETHYLNITROSAMINE ON CELL REPLICATION AND UNSCHEDULED DNA SYNTHESIS IN TARGET AND NONTARGET CELL POPULATIONS IN RAT LIVER FOLLOWING CHRONIC ADMINISTRATION.

Lewis JG, Swenberg JA
(c/o Swenberg), Chemical Industry Inst. Technology, Research Triangle Park, NC, 27790
Cancer Res; 42(1):89-92 1982

Marked differences in the rates of de novo DNA synthesis and unscheduled DNA synthesis were observed in hepatocytes and nonparenchymal cells (NPC) isolated from Fischer 344 rats following in vivo exposure to 1,2-dimethylhydrazine (SDMH) or diethylnitrosamine (DEN) for 1.5, 4, 8, 16, and 28 days. Liver cells were labeled in vivo with bromodeoxyuridine and [3H]thymidine, following which, hepatocytes and NPC were separated by elutriation centrifugation. Purified DNA was then separated into fully replicated and nonreplicated DNA by ultracentrifugation in CsCl gradients. Following exposure to SDMH, the rate of de novo DNA replication in NPC was greatly increased over both control NPC and the corresponding hepatocytes for the entire time course. Unscheduled DNA synthesis was only observed in hepatocytes after exposure to SDMH. Following exposure to DEN, both cell populations exhibited changes in de novo DNA synthesis that were directly proportional to one another except at 1.5 days. Increases occurred first in hepatocytes at 1.5 days but were delayed in NPC until 4 days. Hepatocyte replication returned to control values by 28 days. Unschedule d DNA synthesis was much lower following exposure to DEN than SDMH. Therefore, SDMH, which induces hemangioendotheliomas of the liver at the dose given, induces a marked increase in cell replication in the target cell population and unscheduled DNA synthesis in the resistant cell population. DEN, which induces hepatocellular carcinoma, moderately stimulates cell replication in both liver cell populations and induces little unscheduled DNA synthesis in either population. (Author abstract) (19 Refs)

30. IMMUNOPRECIPITATION ASSAY OF ALPHA-FETOPROTEIN SYNTHESIS BY CULTURED MOUSE HEPATOMA CELLS TREATED WITH ESTROGENS AND GLUCOCORTICOIDS.

Rosebrock JA, Parker CL, Kute TE
(c/o Parker) Dept. Biology, Atlanta Univ., Atlanta, GA, 30314
Differentiation; 19(3):168-178 1981

This investigation was to study the biosynthesis of 3H-labeled alpha-fetoprotein (AFP) by cultured mouse hepatoma (HEPA-2) cells. Both the function and regulation of this oncodevelopmental gene are unknown. However, evidence indicates that mechanisms controlling the expression of AFP involve aspects of both normal embryonic development and neoplastic transformation. The secretion of AFP was analyzed during different phases of the growth cycle to provide information on AFP production using standard culture conditions. the highest rate of secretion occurred during the stationary phase, followed by the late logarithmic and early logarithmic phases of growth, respectively. The production of AFP was then determined following the addition of glucocorticoids and estrogens in an attempt to understand hormonal factors that may be involved. Studies utilizing estradiol-17beta indicated that the secretion of AFP did not appear to be sensitive to this steroid even though sucrose density gradient analysis of HEPA-2 cytosol, for estrogenic receptors, revealed competitive binding moieties in the 8S and 4S regions of the gradient. In contrast, the secretion of the total complement of proteins, including AFP, was significantly stimulated by the glucocorticoids, dexamethasone and corticosterone. Analysis of HEPA-2 cytosol for glucocorticoid receptors revealed binding components in the 7S and 3-4S regions of the gradient. The 3H-dexamethasone binding appeared to be stereospecific since nonlabeled dexamethasone, but not nonlabeled estradiol-17beta, effectively displaced the bound radioactivity. The glucocorticoid-binding component in HEPA-2 therefore displayed characteristics reported for glucocorticoid receptors in normal liver and other hepatomas. (Author abstract) (69 Refs)

REVIEWS AND OTHER RELATED STUDIES

31. REVIEW OF THE HEPATIC RESPONSE TO HYPOLIPIDAEMIC DRUGS IN RODENTS AND ASSESSMENT OF ITS TOXICOLOGICAL SIGNIFICANCE TO MAN.

Cohen AJ, Grasso P
Toxicology Advisory Services, 25 Cedar Road, Sutton, Surrey SM2 5DG, England
Food Cosmet Toxicol; 19(5):585-605 1981

Hypolipidemic agents produce in rodents a hepatic response, characterized by hepatomegaly, proliferation of smooth endoplasmic reticulum, and a marked increase in the number of peroxisomes and changes in the peroxisomal structure and enzyme composition, as well as liver carcinomas. An overview is presented of biochemical, histochemical, histologic, and ultrastructural changes induced in the liver by these agents. Studies concerning the significance of peroxisome proliferation are stressed, and data are critically assessed to ascertain the extent to which drug-induced changes in the rodent liver are relevant in man. Chemically unrelated hypolipidemic compounds that cause both hepatic peroxisome proliferation and liver carcinomas in rats or mice include clofibrate, nafenopin, tibric acid, and phthalate esters. One indication of the importance of peroxisome proliferation in the development of liver cancer in rodents is that, at low doses, when peroxisome proliferation is absent or minimal, liver tumors do not occur. In addition, hypolipidemic drugs exert differential effects on the activities of hepatic peroxisomal enzymes. Striking increases in the activities of enzymes involved in fatty acid oxidation overshadow the small increases in the activities of catalase and certain oxidase enzymes. It is suggested that the bioavailability of catalase in the liver peroxisomes of rodents treated with hypolipidemic drugs is insufficient to detoxify injurious peroxide concentrations resulting from enhanced activity of hydrogen-peroxide-generating enzymes. Thus, liver cells may be exposed to the cytotoxic or DNA-damaging potential of hydrogen peroxide, which could lead to development of neoplasms. Absence of a peroxisomal response in man coupled with differences in the way rodents and humans handle lipoprotein remnants bound to liver cells make it unlikely that chronic administration of hypolipidemic drugs present a liver-cancer risk in man. (93 Refs)

32. LIVER CARCINOGENESIS: THE ROLE FOR SOME CHEMICALS OF AN EPIGENETIC MECHANISM OF LIVER-TUMOR PROMOTION INVOLVING MODIFICATION OF THE CELL MEMBRANE.

Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):577-583 1981

A number of chemicals, including phenobarbitals, DDT, and polychlorinated biphenyl, are hepatocarcinogenic in mice and rats after prolonged exposure; they lack genotoxic action and have been suggested to be epigenetic carcinogens. Because several of these chemicals enhance the effect of genotoxic carcinogens under conditions in which they are not themselves carcinogenic, they are probably of the promoter class of epigenetic carcinogens. Mechanism of promotion may involve (1) completion of conversion of partially transformed cells to full neoplastic cells, or (2) inhibition by the promoter of intercellular com munication. The first mechanism has been demonstrated in skin-tumor promoters (phorbol esters and teleocidin B), whereas the latter mechanism has been demonstrated in studies in which tumor promoters inhibited intercellular communication in fibroblast- and liver-cell cultures. Inhibition by DDT of metabolic cooperation between hepatocytes and adult rat-liver epithelial-thioguanine-resistant mutant cells is described. The theory that tumor promoters interfere with transmission of regulatory factors from normal to spontaneously transformed cells is consistent with the dose-response characteristics of epigenetic promoter hepatocarcinogens. (37 Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.
Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
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7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIO-PATHOGENESIS OF ACUTE LEUKAEMIA.
Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
Sangre (Barc); 26(5B):700-717 1981
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10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

17. GENITAL CANCER AND VIRUSES.
Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
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EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. MALIGNANT TUMORS AFTER CHRONIC EXPOSURE TO VINYL CHLORIDE.

Emmerich KH, Norpoth K
Inst. Pathology, Univ. Munster, Domagkstr. 17, D-4400 Munster, W. Germany
J Cancer Res Clin Oncol; 102(1):1-11 1981

Correlations between exposure to vinyl chloride and the development of malignant tumors in the liver have been known since 1974 and have been confirmed by many an experimental investigation. Based on the evaluation of mortality statistics from nine different countries an increased incidence of malignant tumors of the lung, the gastrointestinal tract, and the central nervous system (CNS), and of malignant lymphomas is documented in connection with exposure to vinyl chloride. Statistically significant increases, however, are only found in the incidence of malignant liver tumors. Metabolism and toxicology of vinyl chloride are discussed in detail. (Author abstract) (78 Refs)

2. FORMATION, OCCURRENCE, AND CARCINOGENICITY OF N-NITROSOAMINES IN TOBACCO PRODUCTS.

Hoffmann D, Adams JD, Brunnemann KD, Hecht SS
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 174():247-273 1981

N-nitrosamines (NNA) formed during processing and smoking of tobacco products are discussed. Tobacco and tobacco smoke contain three types of NNA; volatile nitrosamines (VNA), NNA deriving from residues of agricultural chemicals on tobacco, and the tobacco specific nitrosamines (TSNA). VNA can be selectively reduced in cigarette smoke by cellulose acetate filter tips. The animal carcinogen nitrosodiethanolamine (NDELA) was detected in the concentrations of 0.1-6.8 ppm in tobacco and 10-40 nanog/cigarette in the smoke. NDELA induces carcinoma of the liver and kidney in rats, and carcinoma of the nasal cavity and papillomas of the trachea in hamsters. TSNA concentrations range is 1-100 ppm in tobacco and 1-10 ug/cigarette in the cigarette smoke. Reduction in tobacco smoke can be achieved by cellulose acetate filters and perforation of the filter tip. In mice, rats, and hamsters N-nitrosonornicotine is moderately active while 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a strong carcinogen. Carcinogenicity of N-nitrosoanatabine is under investigation. (50 Refs)

3. CONTRACEPTIVES AND THE LIVER.

Schmid M
Medizinische Klinik, Stadtspital Waid, Tiechestr. 99, CH-8037 Zurich, Switzerland
Leber Magen Darm; 11(5):216-226 1981

Studies on the relationships between the use of oral contraceptives (OC) and hepatic diseases are reviewed. The relationship between the long-term use of OC and benign hepatocellular adenoma is now beyond doubt. The progestagen component of the ovulation inhibitor acts as an enzyme inducer which may facilitate the formation of carcinogenic metabolites from various substances, and prompt elimination of these metabolites with the bile is prevented by the cholestatic effect of the estrogens. The relationship between OC and focal nodular hyperplasia is less evident. Here, the congenital hamartomatosis represents a site of least resistance for the hormones, but the steroid hormones are probably responsible for the vascular complications, especially for peliosis. Malignant hepatic tumors (hepatocellular carcinoma and especially hepatoblastoma and angiosarcoma) in connection with the long-term use of OC are extremely rare. The alpha-fetoprotein level is usually not increased significantly in patients with hepatocellular adenoma and carcinoma due to OC. (52 Refs) (In GER)

4. HEPATIC LESIONS CAUSED BY ANABOLIC AND CONTRACEPTIVE STEROIDS.

Ishak KG
Dept. Hepatic Pathology, Armed Forces Inst. Pathology, Washington, DC
Semin Liver Dis; 1(2):116-128 1981

The pathobiology of hepatic lesions induced by long-term use of contraceptive (CS) or anabolic (AS) steroids is described. Lesions attributable to CS and AS may involve any of the systems of the liver, from the bile canaliculi to the hepatocyte to the vessels supplying and draining blood. Oral contraceptives have a number of physiologic effects upon the liver which include decreased bile flow, diminished secretion of organic anions and decreased synthesis and secretion of bile acids. Estrogens and progestins can increase the activity of many enzymes and alter the concentration of many plasma proteins. Subcellular alterations have been reported in humans and rats on AS and women on CS and involve multiple organelles of the several systems of the liver. Both AS and CS have been implicated in intrahepatic cholestasis, and in vascular complications including sinusoidal dilatation, peliosis hepatis, and Budd-Chiari syndrome. AS and CS have been associated with diffuse hyperplasia, nodular transformation, focal nodular hyperplasia, hepatocellular adenoma, hepatocellular carcinoma, and miscellaneous malignant tumors. Nonneoplastic effects include potentiation of preexisting liver disease, cholelithiasis, and pancreatitis. (167 Refs)

5. WHO WORLD CAMPAIGN AGAINST CANCER: ONE CASE OF CANCER IN THREE CAN BE PREVENTED. PRIORITY OF FIGHT AGAINST FOUR TUMOR TYPES.

Stjernsward J
WHO Cancer Unit, Geneva, Switzerland
Lakartidningen; 78(46):4128-4130 1981

Based on the knowledge of cancer-causing agents and circumstances, the Committee on Cancer of World Health Organization has given priority to the battle against four types of cancer, which can be prevented by eliminating their causes. They include cancer of the mouth, lungs, liver, and uterine cervix. Chewing of tobacco and betel is a major cause of cancer of the mouth. Cigarette smoking is the principal cause of lung cancer in developed countries, but the incidence of smoking is increasing in third world countries, which may lead to a corresponding increase in lung cancer incidence there. Hepatitis B virus is a major cause of primary liver cancer along with aflatoxins. Reduction of the incidence of cancer of the uterine cervix is expected from better genital hygiene. (no Refs) (In SWE)

TUMOR INDUCTION IN ANIMALS

6. BLASTOGENIC EFFECT OF TREATMENT WITH LOW CONCENTRATIONS OF NITROSODIMETHYLAMINE, DIMETHYLAMINE AND NITROGEN DIOXIDE.

Benemanskii VV, Prusakov VM, Leshchenko ME
USSR
Vopr Onkol; 27(10):56-62 1981

The round the clock inhalation of the mixture of nitrosodimethylamine (NDMA), di methylamine (DMA) and nitrogen dioxide, with NDMA concentrations varying within 0.66-0.0026 mg/m3, was followed by development of tumors in the kidney, liver, lungs and at other sites in albino noninbred rats, after a yr of exposure. Application of DMA and nitrogen dioxide modified the carcinogenic effect of NDMA. In male rats, the blastogenic effect of the mixture was higher, as compared with that of inhalation, of NDMA alone. NDMA inhalation resulted in a lower tumor yield in female rats. (Author abstract) (19 Refs) (In RUS)

7. THE ROLE OF AGING IN N-NITROSODIMETHYLAMINE- AND N-DIMETHYLNITRAMINE-INDUCED CARCINOGENESIS IN AMPHIBIA.

Khudolei VV
N. N. Petrov Res. Inst., Oncology USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(10):67-71 1981

A comparison of the reactions of adult and juvenile amphibians Rana temporaria showed that the host sensitivity (latency and tumor incidence) of both groups of animals to the carcinogenic action of N-nitrosodimethylamine and dimethylnitramine was of the same order. However, a 'shift' in organ sensitivity (different organotropic effect) was observed. The predominance of hepatocellular cancer in adult and hemocytoblastosis in young Rana temporaria was significant (p less than 0.01). The mechanisms of these 'shifts' are unknown, but a role of the metabolic and reparative processes has been suggested. (Author abstract) (18 Refs) (In RUS)

8. CARCINOGEN BIOASSAY OF ENFLURANE IN MICE.

Baden JM, Egbert B, Mazze RI
Anesthesiology Service, 112A, Veterans Admin. Medical Center, Palo Alto, CA, 94304
Anesthesiology; 56(1):9-13 1982

A carcinogen bioassay of enflurane was performed in Swiss/ICR mice. Two groups of weanling mice, each of 125 males and 125 females, were exposed to either a maximum tolerated dose of enflurane, 3,000 ppm (0.3% v/v) or compressed air for 4 hr per day, 5 days per wk. After 52 wk exposure, 25 males and 25 females from each group were killed. After 78 wk exposure, a 4-wk period without treatment was allowed before the remaining mice were killed. Mice killed at the scheduled periods and those killed or dying at other times throughout the study, underwent extensive gross and histologic examination unless autolysis or cannibalism precluded examination. After 78 wk exposure, male mice in the enflurane-treated group had a 36% incidence of liver tumors compared with 24% in the control group; however, the difference was not statistically significant. The incidence of lung tumors was about 20% in all groups. Other neoplastic lesions occurred in small numbers and were unrelated to treatment. It was concluded that under the conditions of the present experiment, chronic administration of enflurane at its maximum tolerated dose did not lead to an increased incidence of neoplasia in Swiss/ICR mice. (Author abstract) (9 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

9. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS: SUMMATION VERSUS PROMOTION EFFECTS.

Williams GM, Katayama S, Ohmori T
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1111-1117 1981

A comparative study was made of the sequential administration of the liver carcinogen, diethylnitrosamine (DEN), or the liver tumor promoter, phenobarbital, given after the liver carcinogen, N-2-fluorenylacetamide (FAA). The effects of the second carcinogen on preneoplastic cellular lesions induced by the first carcinogen were comparable to the effects of the promoter. In addition, both sequential exposures enhanced the ultimate carcinogenic effect, although the combination of FAA followed by DEN resulted in a greater number of malignant neoplasms. Thus, enhancement of carcinogenesis by a second chemical cannot be used by itself as evidence of a promoting action. Approaches to the more precise definition of promoters include exclusion of genotoxicity, identification of epigenetic mechanisms and lack of a summation effect with administration prior to genotoxic carcinogens. (Author abstract) (50 Refs)

10. EFFECT OF BOLANDIOL DIPROPIONATE (ANABIOL), AN ANABOLIC HORMONE, ON DIETHYLNITROSAMINE-INDUCED HEPATOCARCINOGENESIS IN RATS.

Mochizuki Y, Sawada N, Furukawa K
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Nishi-17-chome, Minami-1-jo, Chuo-ku, Sapporo 060, Japan
Gan; 72(6):969-973 1981

The effect of bolandiol dipropionate (Anabiol), an anabolic steroid hormone, on hepatocarcinogenesis was investigated in rats. Anabiol was injected at a dose of 5 mg into the thigh muscle at intervals of 2 wk, simultaneously with or subsequently to the 4-wk administration of diethylnitrosamine (DEN). The average number of tumors larger than 3 mm in diameter per rat in the subsequently treated group at 25 wk after commencement of DEN was significantly increased and the number of tumors larger than 5 mm in diameter per rat in the simultaneously treated group was significantly increased, when compared with that in the group given DEN alone. Thus, the enhancing effect of Anabiol on hepatocarcinogenesis was evident in terms of tumor size, regardless of whether the hormone was given simultaneously with or subsequently to the carcinogen. (Author abstract) (24 Refs)

11. SEX DIFFERENCE IN ENHANCEMENT OF GGTASE-POSITIVE FOCI BY HEXACHLOROBENZENE AND LINDANE IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U. S. Environmental Protection Agency, Cincinnati, OH, 45268
Cancer Lett; 15(1):95-101 1982

The ability of hexachlorobenzene (HCB) and lindane (LN) in diethylnitrosamine (DENA) pretreated rats to enhance the incidence of gamma-glutamyltranspeptidase (GGTase)-positive foci was determined. Male and female Sprague-Dawley rats (175-225 g) were used in the experiments. HCB and LN increased the incidence of DENA and initiated GGTase-positive foci in rat liver. Animals that received a partial hepatectomy or sham operation, and then were given HCB or LN in their diet, developed relatively few GGTase-positive foci. When DENA was administered 24 hr after the partial hepatectomy, as compared to the sham operation, there was a slightly increased incidence of GGTase-positive foci. In female rats that received either a partial hepatectomy or sham operation followed by DENA, HCB and LN increased the incidence of GGTase-positive foci. In male rats, HCB and LN increased the incidence of GGtase-positive foci only when a partial hepatectomy preceded the DENA. The enhancement of GGtase-positive foci by HCB and LN was greater in female, compared to male rats. The results suggest that hepatocarcinogenicity of HCB and LN results in tumor promotion. (33 Refs)

12. EFFECT OF NEONATAL CASTRATION ON LIVER TUMOR INDUCTION BY N-2-FLUORENYLACETAMIDE IN SUCKLING BALB/C MICE.

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Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia
Carcinogenesis; 2(11):1219-1221 1981

BALB/c mice were castrated at 2 days of age and control animals were sham-operated. Untreated male and female mice were also included for comparison. One-half of the mice in each group were fed on alternate days with 1.5% N-2-fluorenylacetamide suspended in 1% gelatine by stomach tube beginning 1 wk of age for a total of 14 feedings. The experiment was terminated when the mice reached 1 yr old. Approx 30% of the male mice, but none of the females, developed liver tumors in groups fed carcinogen. This male predominance in the incidence of hepatocellular carcinomas was completely abolished when the animals were castrated neonatally. No lesions were observed in the liver of mice treated with gelatine suspension alone except one with neoplastic nodule. Although it has been observed that liver tumors are produced more readily in younger than in older mice, the present investigation shows that male hormonal environment during early life is more important than the age on the development of liver tumors initiated by carcinogen. (Author abstract) (21 Refs)

13. STIMULATION OF DNA SYNTHESIS AND CELL PROLIFERATION IN THE LIVER OF RATS FED A CHOLINE-DEVOID DIET AND THEIR SUPPRESSION BY PHENOBARBITAL.

Abanobi SE, Lombardi B, Shinozuka H
Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Cancer Res; 42(2):412-415 1982

Feeding of a choline-devoid (CD) diet and dietary administration of phenobarbital (PHB) are efficient promoters of liver carcinogenesis in the rat. Furthermore, inclusion of PHB in a CD diet results in a synergistic effect, inasmuch as the promoting action of their combination is greater than the sum of those exerted by either agent alone. To investigate the mechanism(s) of action of the two promoters, liver DNA synthesis and liver cell proliferation were studied in rats fed a CD diet, a choline-supplmented diet, or the same diets to which 0.06% PHB was added. DNA synthesis was determined by [3H]thymidine incorporation into DNA and autoradiography, and cell proliferation was determined by mitosis counts. Feeding the CD diet caused an increase of both DNA synthesis and cell proliferation over those present in rats fed the choline-supplemented diet. Inclusion of PHB in the CD diet, on the other hand, inhibited DNA synthesis and cell proliferation. These results indicate that stimulation of cell proliferation per se may not be a sufficient condition for an agent to act as a promoter of liver carcinogenesis. (Author abstract) (32 Refs)

14. DIAPLACENTAL INITIATION OF NMRI MICE WITH 7,12-DIMETHYL-BENZ[A]ANTHRACENE DURING GESTATION DAYS 6-20 AND POSTNATAL TREATMENT OF THE F1-GENERATION WITH THE PHORBOL ESTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE: TUMOR INCIDENCE IN ORGANS OTHER THAN THE SKIN.

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Carcinogenesis; 2(11):1087-1094 1981

The tumor spectrum and tumor incidence in organs other than the skin were investigated in the 12-O-tetradecanoylphorbol-13-acetate (TPA) treated F1-generation of 13 groups of NMRI mice which had been initiated by a single intragastric dose of 7,12-dimethylbenz[a]anthracene during Days 6,8, and 10-20 of pregnancy. Promotion by topical application of TPA to the back skin was carried out twice per wk 12 wk after birth over a period of 26 wk. The forestomach epithelium represented the only organ in which statistically significant 2-stage carcinogenesis could be demonstrated. A promotion effect could be seen in tumors of the Harderian gland, of the liver of male animals and on the development of both benign and malignant tumors of the lung in both sexes. Promotion treatment therefore led to an activation of initiated tumor cells in those organs in which a very sensitive, more or less narrowly spaced oncogenic determination period exists. (Author abstract) (12 Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

15. EFFECTS OF STRUCTURE ON THE CARCINOGENIC BEHAVIOR OF NITROSAMINES.

Wishnok JS
Dept. Nutrition and Food Sciences, Massachusetts Inst. Technology, Cambridge, MA, 02139
ACS Symp Ser; 174():77-87 1981

Small, closely-related series of nitrosamines have been examined and a quantitative structure-activity model (QSM) based on molecular descriptors (physicochemical, geometrical, topological, and electronic) has been developed. The final form of QSM can be interpreted in terms of the proposed mechanisms of action or of modified aspects of these mechanisms. Nitrosamines are highly sensitive towards one or a few target organs. Test compounds included 13 dialkylnitrosamines which induced tumors in the liver or in the lung or esophagus. All test compounds were administered at equal daily doses. Relative properties of compounds reflect then only the differences in the molecular structure of the test substances. The model for organ selectivity requires terms for the parent nitrosamine as well as for the hypothesized metabolites while the model for potency variations contains terms only for the unmetabolized parent compound. (29 Refs)

16. METABOLIC FATE OF ASYMMETRIC N,N-DIALKYLNITROSAMINES HAVING A BUTYL GROUP IN THE RAT.

Suzuki E, Okada M
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Gan; 72(6):910-920 1981

The metabolic fate of N-alkyl-N-butylnitrosamines (alkyl=ethyl, propyl, and pentyl), which induce tumors in the liver and esophagus but do not induce bladder tumors, was investigated in the rat, in order to elucidate any possible correlation between metabolism and the noncarcinogenicity to the urinary bladder of these N-nitrosamines. They were extensively metabolized in the rat, no unchanged compounds being found in the urine. The metabolic pattern of these N-nitrosamines having a butyl chain was essentially similar to that of N,N-dibutylnitrosamine, which induces tumors in the bladder as well as in the liver and esophagus. They were mainly metabolized via omega-oxidation followed by beta-oxidation and/or (omega-1)-oxidation of either of the two alkyl chains. Thus the N-alkyl-N-(3-carboxypropyl)nitrosamine and/or the N-alkyl-N-(2-carboxyethyl)nitrosamine were identified as the principal urinary metabolites. Possible important factors concerned with the induction of bladder tumors by N,N-dialkylnitrosamines are discussed from the metabolic point of view. (Author abstract) (21 Refs)

17. INTERINDIVIDUAL VARIATION OF CARCINOGEN ACTIVATION BY HUMAN LIVER HOMOGENATES: A STUDY USING DIMETHYLNITROSAMINE (DMN) AND CYCLOPHOSPHAMIDE (CP) AS PRECURSOR GENOTOXIC AGENTS AND CLASTOGENICITY AND INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER V79-E CELLS AS ENDPOINTS.

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Arch Geschwulstforsch; 52(2):97-104 1982

Interindividual variation in activation of carcinogens by liver homogenates (LH) from six kidney donors was studied. Liver tissue was homogenized and centrifuged at 9,000 gravities. Similar LH were made from livers of inbred rats of strain E. Mixtures of LH supernatants (S-9) and exponentially growing, asynchronous Chinese hamster V79-E cells were exposed to dimethylnitrosamine (DMN) or cyclophosphamide (CP) for 3 hr. Human S-9 alone produced no abnormalities in V-79-E cells. With 10(-2) DMN human S-9 produced 43.7% abnormal metaphases (AM), with a 1.3-fold variation among individuals; 3.46 sister chromatid exchanges (SCE)/chromosome were produced, with a 1.3-fold variation. With the same level of DMN, rat S-9 produced 35% AM and 3.58 SCE/chromosome. With 10(-3) M CP human S-9 produced AM ranging from background levels to complete cell killing; SCE ranged from 1.33-7.35/chromosome. With 10(-4) M CP, rat S-9 produced 16% AM and 2.82 SCE/chromosome. With 10(-3) M CP, rat S-9 produced total cell killing. Results indicate that human LH activate DMN to approx the same extent as rat LH, but that activation of CP by human LH is much more varied. (33 Refs)

18. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

Acosta D, Mitchell DB
Dept. Pharmacology, Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of xenobiotics to toxic intermediates and to study the mechanism(s) by which these chemicals produce cellular injury. This model was employed to investigate the cytochrome P-450 mediated biotransformation of cyclophosphamide (CP) to cytotoxic metabolites that nonspecifically alkylate DNA and cellular proteins. The parenchymal cells were isolated by an in situ collagenase perfusion technique and cultured for 24 hr prior to drug treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-3) M for 24 hr. Initial studies indicated minimal toxicity to non-replicating parenchymal hepatocytes maintained in ornithine-supplemented, arginine-deficient medium. The addition of arginine permitted the overgrowth of fibroblasts in the same culture system. These fibroblasts then became the target of alkylating CP metabolites produced by the parenchymal cells. By day 3 after CP administration, cell number and total protein per dish decreased by over 40%. The morphology of the cultures changed dramatically because of fibroblast destruction. The cytotoxicity to dividing fibroblasts was eliminated by administering 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A), an inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reacting aliquots of medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. These results provide both direct and indirect evidence of drug metabolism in cultured cells and suggest that this co-culture system can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

19. GENETIC EVIDENCE FOR MANY UNIQUE LIVER MICROSOMAL P-450-MEDIATED MONOOXYGENASE ACTIVITIES IN HETEROGENEIC STOCK MICE.

Lang MA, Gielen JE, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12068-12075 1981

Total cytochrome P-450 content, the Soret maximum of the reduced P-450-CO complex, NADPH-cytochrome c reductase activity, and 20 monooxygenase activities were determined in liver microsomes from each of 12 individual Heterogeneic Stock (HS) mice at varying times after 3-methylcholanthrene treatment. The choice of genetically very heterogeneous mice and the possibility of different turnover rates (synthesis/degradation) during the 3-methylcholanthrene induction process provided us with a strong likelihood of detecting differences in drug-metabolizing enzyme activities. Such diversity would also be expected among the human population. The substrates included benzo[a]pyrene, ethoxyresorufin, biphenyl, p-nitroanisole, 2-acetylaminofluorene, 7-ethoxycoumarin, zoxazolamine, estradiol-17beta, testosterone, progesterone, pregnenolone, dehydroepiandrosterone, and aldrin. By two-factor analysis of variance, 18 unique liver microsomal monooxygenase activities appear to be distinctly different from one another, out of the 20 activities chosen for study. Ethoxyresorufin O-deethylase activity is significantly correlated ($p = 0.11$) with aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Dehydroepiandrosterone 16alpha-hydroxylase activity correlates well with the testosterone ($p = 0.33$), progesterone ($p = 0.16$), and pregnenolone ($p = 0.11$) 16alpha-hydroxylases. Testosterone 16alpha-hydroxylase, progesterone 16alpha-hydroxylase, and pregnenolone 16alpha-hydroxylase activities, on the other hand, are all significantly (p less than 0.001) different from one another. These data with intact microsomes illustrate the complexity of the problem with multiple P-450-mediated monooxygenases. Almost every activity therefore appears to be unique and probably reflects the aggregate contribution from numerous forms of P-450. (Author abstract) (33 Refs)

20. ACTIVATION OF BENZO(A)PYRENE AND 2-ACETAMIDOFLUORENE TO MUTAGENS BY MICROSOMAL PREPARATIONS FROM DIFFERENT ANIMAL SPECIES: ROLE OF CYTOCHROME P-450 AND P-448.

Ioannides C, Parkinson C, Parke DV
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Xenobiotica; 11(10):701-708 1981

The metabolic activation of benzo(a)pyrene and 2-acetamidofluorene to mutagens was studied with liver microsomal preparations from rat, guinea-pig, hamster and mouse, untreated or pretreated with phenobarbitone or 3-methylcholanthrene. Liver microsomal preparations from all animal species a ctivated benzo(a)pyrene, that from mouse being the most efficient. Similarly, microsomal preparations from guinea-pig, hamster and mouse could activate 2-acetamidofluorene, but that from rat exhibited very weak activity. Activation of benzo(a)pyrene into mutagenic intermediates by liver microsomal preparations was increased for all animals except mouse by pretreatment with 3-methylcholanthrene. In contrast, pretreatment with phenobarbitone decreased the activation by microsomal preparations from all species. Activation of 2-acetamidofluorene by liver microsomal preparations from rat and guinea-pig, but not mouse and hamster, was increased by pretreatment of the animals with phenobarbitone. Pretreatment with 3-methylcholanthrene decreased the activation of this carcinogen by microsomal preparations from all species. The metabolic activation of benzo(a)pyrene is catalyzed by cytochrome P-448 but not cytochrome P-450. The activation of 2-acetamidofluorene to mutagens may involve, in addition to the mixed-function oxidases, other microsomal enzyme systems. (Author abstract) (29 Refs)

21. PRESENCE OF BENZO[A]PYRENE METABOLIZING ACTIVITIES IN ISOLATED RAT LIVER NUCLEOLI.

Lafarge-Frayssinet C, Alexandrov K, Rimbaut C, Dansette PM, Mousset S, Frayssinet C
Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94802 Villejuif Cedex, France
Carcinogenesis; 2(11):1189-1193 1981

A benzo[a]pyrene (B[a]P) hydroxylase activity and epoxide hydrolase (EH) activity have been found in rat liver nucleoli obtained from untreated (C) and 3-methylcholanthrene (3-MC) pretreated rats. A comparison of the enzyme activities was made in rat nuclei and nucleoli. Light and electron microscopic observations of nucleolar preparations did not reveal significant contamination either by intact nuclei or by nuclear membranes, and glucose 6-phosphatase, a marker of microsomal activity, was not detected in our nucleolar preparations. NADPH cytochrome c-reductase could be measured in C and 3-MC nuclei and very low but detectable activity was found in the nucleoli. Nucleolar preparations revealed significant hydroxylating activity, which was inducible by 3-MC in nuclei but not in nucleoli. The presence of EH in nucleoli was demonstrated with phenanthrene 9,10-oxide and B[a]P 4,5-oxide, but the nucleolar activities were lower than those obtained using intact nuclei. The addition of 1,1,1-trichloropropene 2,3-oxide completely inhibited EH activity. Furthermore the presence of covalently-bound metabolites of B[a]P formed in isolated nucleoli was demonstrated by cytofluoromicroscopy. (Author abstract) (30 Refs)

22. COVALENT BINDING OF BENZO(A)PYRENE TO DNA IN FISH LIVER.

Varanasi U, Stein JE, Hom T
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Biochem Biophys Res Commun; 103(2):780-787 1981

The extent of covalent binding of benzo(a)pyrene (BaP) intermediates to hepatic DNA and protein was determined in English sole exposed po to 3H-BaP. Radioactivity in the liver represented 0.6% of the administered dose at 16 hr. The liver concentration of BaP-derived radioactivity did not change significantly from 16-336 hr after BaP administration; greater than 98% of the total radioactivity in liver was in the form of the organic solvent- and water-soluble metabolites. Detectable binding of BaP intermediates to liver DNA was observed between 6 and 336 hr after BaP exposure. No statistically significant change was observed in the binding values for DNA during the 2 wk exposure; the extent of BaP binding to liver protein did not change significantly over the 2 wk period. The av of all specific activity values for protein (58 +-51) was not significantly different from the av value for DNA (44 +-39). The results indicated that the extent of BaP binding to fish liver DNA is comparable to values reported for mammalian tissues susceptible to polycyclic aromatic hydrocarbon-induced neoplasms; chemical modification of hepatic DNA was observed for at least 2 wk after a single exposure to BaP. (30 Refs)

23. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

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Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

24. HISTOCHEMICAL FINDINGS SUGGESTING THAT METHYLAZOXYMETHANOL, A LIVER AND KIDNEY CARCINOGEN, IS A SUBSTRATE FOR HEPATIC AND RENAL CHOLINE DEHYDROGENASE.

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Carcinogenesis; 2(11):1135-1139 1981

The potent carcinogen, Methylazoxymethanol (MAM), induces tumors predominantly in rat liver, colon and kidney. The findings reported in this paper suggest that MAM is a substrate for the enzyme choline dehydrogenase located in rat hepatocytes and in the terminal portion of the renal proximal convoluted tubule. As with the natural substrate choline, this reaction with MAM did not require NAD+, was not inhibited by pyrazole and was dependent on the electron transfer reagent, phenazine methosulfate. The product of this reaction is probably the same as that obtained from the metabolism of MAM by alcohol dehydrogenase, namely, an unstable aldehydic derivative which decomposes rapidly to carbonium ions. The reaction with alcohol dehydrogenase offered an explantation for the organotropic effects of this carcinogen in liver and colon and the current report provides a mechanism for the induction of kidney tumors as well as another possible means for production of liver tumors. (Author abstract) (16 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

25. PRIMARY HEPATOCELLULAR CARCINOMA -- ETIOLOGY, PATHOGENESIS, AND PREVENTION.

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Hum Pathol; 12(12):1085-1097 1981

Worldwide, primary hepatocellular carcinoma may be the most common cancer in men. Usually it occurs in association with cirrhosis or chronic hepatitis. In this article I present evidence that the majority of these cases are associated with, and probably caused by, persistent infection with hepatitis B virus. I also propose a model that describes the role of the hepatitis B virus in the pathogenesis of primary hepatocellular carcinoma. If persistent infection with hepatitis B virus is required for the development of most cases of primary hepatocellular carcinoma, prevention of such infections should prevent most cases of primary hepatocellular carcinoma. A vaccine against hepatitis B virus, prepared from surface antigen particles (HBsAg) harvested from the blood of hepatitis B virus carriers, has been safe and effective in preventing acute infection with hepatitis B virus in adult homosexual men. If it is equally safe and effective in young children, it will be administered widely to populations living in areas endemic for hepatitis B virus infections. Thereafter it may be possible to learn within 5 to 10 years whether the vaccine prevents chronic liver disease. If it does, it will be reasonable to conclude that it will also prevent primary hepatocellular carcinoma. (Author abstract) (47 Refs)

26. THE HEPATITIS-B VIRUS AND HEPATOCELLULAR CARCINOMA.

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Dept. Medicine, Witwatersrand Univ. Medical Sch., Johannesburg, South Africa
Semin Liver Dis; 1(1):59-67 1981

The association between hepatocellular carcinoma (HCC) and chronic hepatitis-B virus (HBV) is discussed, and various explanations for its etiology are considered. The world-wide geographic distributions of the HBV carrier state and HCC are remarkably similar, with some exceptions. Countries in sub-Saharan Africa and the Far East, eg, with HBV surface antigen carrier rates of 6-14% also have the highest rates of HCC. However, in Greenland, where 7-25% of the population has chronic HBV surface antigen, HCC is nevertheless rare. This discrepancy could be explained by the absence of a cocarcinogen in the Greenland environment. The most persuasive evidence that an association exists between HCC and HBV is the frequency with which markers of the virus are present in the serum and tissues of patients with this tumor. Alternative explanations to a cause and effect relationship between HBV infection and HCC are discussed. However, no such considered explanations account for the association as well as the postulate that HBV plays a causal role in HCC. (84 Refs)

27. A CONTROLLED STUDY OF HEPATITIS CORE ANTIBODY (HBCAB) IN PRIMARY HEPATOCELLULAR CARCINOMA AND LIVER CIRRHOSIS IN KENYA.

Bowry TR, Shah MV, Ahmad Z
Immunology Section, Dept. Human Pathology, Univ. Nairobi, Nairobi, Kenya
East Afr Med J; 58(8):576-582 1981

Incidence of hepatitis B virus (HBV) markers was studied in 75 Kenyan patients with confirmed liver disease. Among these patients, 15 had liver cirrhosis (LC), 13 had LC and concomitant primary hepatocellular carcinoma (PHC), and 47 had PHC. Presence of hepatitis B surface antigen (HBsAg) was detected in 40% of the patients with LC, in 47% of the patients with LC + PHC, and in 46% of the patients with PHC. Among the HBsAg-positive patients, high titers of hepatitis B core antibody (HBcAb) were detected in 100% of the patients with LC, 100% of those with LC + PHC, and 90% of those with PHC. HBcAb as a sole marker of HBV was detected in 13% of the patients with LC, 31% of those with LC + PHC, and 9% of those with PHC. (16 Refs)

28. SEROLOGIC PROFILE AND POSSIBLE ETIOLOGIC FACTORS IN PRIMITIVE CARCINOMA OF THE LIVER.

Caporaso N, Giardullo N, Servillo F, Del Vecchio-Blanco C, Coltorti M
Istituto di Semeiotica Medica, I Facolta di Medicina e Chirurgia, Universita di Napoli, Napoli, Italy
Fegato; 27(1):55-57 1981

The relationship between primitive carcinoma of the liver (PCL) and chronic infection with virus B (CIVB) was studied using radioimmunoassay. CIVB seems to play an important role in the etiology of PCL, especially in areas of high incidence of CIVB. Of 612 patients with evolutive liver pathology, 32 (36-83 yr old, 27 men and 5 women) had PCL. In 23 patients PCL was associated with cirrhosis (ALC); of these 9 had acute progressive hepatitis, 6 were alcoholics, and 7 had blood relatives who had died from PCL. Diagnosis was confirmed by biopsy (obtained through laparoscopy), scintigraphy, alpha1-fetoprotein, and routine blood chemistry. Nine patients had negative results for all serological markers, 11 had positive results for HBsAg+, 4 for anti-HBc+, and 8 for both anti-HBc+ and anti-HBs+. Of the 11 HBsAg+ positive cases, only 2 were associated with 'e' positive results, indicating that the infection with virus B had occurred long ago. No patients reported exposure to toxic industrial products, or contaminated food, or prolongued use of sexual hormones or their derivatives. PCL was frequently associated with CIVB even in non-ALC cases. (5 Refs) (In ITA)

29. ROLE OF ONCOGENES IN THE DEVELOPMENT OF TUMORS.

Klein G
Institutionen for tumorbiologi, Karolinska institutet, Stockholm, Sweden
Lakartidningen; 78(41):3575-3577 1981

Recent studies in viral oncogenes are reviewed. The coupling of some normal genes is a common feature of all tumor transformation processes caused by not directly-transforming RNA tumor viruses. Unlike the RNA viruses, the DNA viruses belong to several greatly different groups. Production of the so-called T antigen is a common feature of all DNA tumor viruses. This antigen occurs in all transformed cells. There are at least three virus types (papilloma virus, Epstein-Barr virus (EBV), and hepatitis B virus) that contribute to the development of certain human tumors, but their contributions are less direct than in the case of infectious diseases. Only papilloma virus induces tumors directly, and most of them are benign, but papilloma virus may play a certain role in the genesis of some malignant epithelial tumors as well. Hepatitis B virus first causes liver cirrhosis, a precancerous state, the development of the tumor clone being the result of abnormal regeneration. (7 Refs) (In SWE)

30. CLINICAL CLASSIFICATION OF HEPATOMA IN JAPAN ACCORDING TO SERIAL CHANGES IN SERUM ALPHA-FETOPROTEIN LEVELS.

Matsumoto Y, Suzuki T, Asada I, Ozawa K, Tobe T, Honjo I
Dept. Surgery, Kohka Medical Center, Minakuchi, Shiga, 528, Japan
Cancer; 49(2):354-360 1982

Quantitative determinations of serum alpha-fetoprotein (AFP) in 96 patients with hepatomas have demonstrated three main groups based on changes in the serial levels: (1) patients with more than 10,000 ng/ml or more in a wk (Group A); (2) patients with levels varying from 200 to 10,000 ng/ml and with an increase of 1,000 ng/ml in 3 to 4 mo (Group B); and (3) patients with serum AFP levels below 200 ng/ml during most of their clinical course (Group C). The patients in Group A had a mean survival time of 7.62 +-3.97 mo, and those in Group B, 16.18 +-12.18 mo. The patients in Group C were subdivided into two groups according to whether survival time was long (33.92 +-28.22 mo) or short (3.75 +-0.87 mo). Histologic findings revealed poorly differentiated carcinoma in patients in Group A, moderately differentiated carcinoma in those in Group B, and well differentiated carcinoma in those with long survival in Group C and anaplastic carcinoma in those with short survival in Group C. (Author abstract) (15 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

31. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

Lindahl R, Evces S, Sheng WL
Biochemistry Program, Univ. Alabama, University, AL, 35486
Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AIDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AIDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare the effects of a variety of tumor induction protocols on the AIDH phenotype. No change in the AIDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen or promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AIDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AIDH phenotype. No correlation exists between tumor size and the degree of deviation of the AIDH phenotype from normal. Nor is there any correlat ion between the degree of AIDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AIDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AIDH phenotype. (Author abstract) (22 Refs)

32. STUDIES ON GLUCOSE-6-PHOSPHATE, FRUCTOSE-1,6-DIPHOSPHATASE ACTIVITY, GLYCOGEN DISTRIBUTION AND ENDOPLASMIC RETICULUM CHANGES DURING HEXACHLOROCYCLOHEXANE INDUCED HEPATOCARCINOGENESIS IN PURE INBRED SWISS MICE.

Karnik AB, Thakore KN, Nigam SK, Babu KA, Lakkad BC, Bhatt DK, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad - 380 016, India
Neoplasma; 28(5):575-584 1981

Inbred Swiss mice were fed hexachlorocyclohexane (BHC) at 500 ppm dose level in diet for 2, 4, 6 and 8 months. Later BHC was discontinued for 4 months and subsequently the animals were refed BHC for 1 month. Glucose-6-phosphatase (G6Pase) and fructose-1,6-diphosphatase (FDPase) activity was studied at different time intervals accompanied with changes in glycogen distribution and endoplasmic reticulum (ER) proliferation in hepatocytes. G6Pase and FDPase showed a decline in activities on BHC feeding. The activities of these enzymes showed recovery on BHC discontinuation. The changes were progressive with duration of exposure. After 6 months exposure the biochemical changes became more resistant to recovery. Maximal changes occurred in 8 month-exposure and the changes were irreversible. Glycogen accumulation and depletion followed a definite pattern. After 2 months of BHC feeding, increase in parenchymal glycogen storage zones was observed. In the later stage of hepatocarcinogenesis and especially in tumors, glycogen was depleted considerably. Smooth endoplasmic reticulum (SER) proliferation was recorded around the 3rd and 4th month. The correlation between glycogen accumulation, SER proliferation, G6Pase and FDPase activity is discussed. (Author abstract) (31 Refs)

33. SEQUENTIAL HISTOCHEMICAL CHANGES IN THE DISTRIBUTION OF ALKALINE PHOSPHATASE IN THE HEXACHLOROCYCLOHEXANE (HCCH) INDUCED LIVER TUMOURS IN PURE INBRED SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Babu KA, Karnik AB, Thakore KN, Kashyap SK
Natl. Inst. Occupational Health, Meghani Nagar, Ahmedabad 380 016, India
Cell Mol Biol; 27(2/3)[illegible]31-238 1981

Inbred Swiss mice were given 500 ppm of technical grade hexachlorocyclohexane (HCCH) in the diet for 2, 4 and 6 mo. Their livers were investigated histochemically for alkaline phosphatase activity. After two mo of exposure the alkaline phosphatase activity has increased on the bile canaliculi and on the plasma membrane. The neoplastic nodules, after 4 mo exposure, have revealed very strong alkaline phosphatase activity, compared to normal areas. The activity remained intense in the tumor even after 6 mo feeding of HCCH; the activity at the plasma membrane level has disappeared in normal part of the tumor-bearing liver. The functional significance of alkaline phosphatase distribution at different locales has been discussed. (Author abstract) (32 Refs)

34. MORPHOLOGY OF EARLY CHANGES IN LIVER CARCINOGENESIS INDUCED BY METHAPYRILENE.

Reznik-Schuller HM, Lijinsky W
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Arch Toxicol; 49(1):79-83 1981

Two wk of treatment with the liver carcinogen methapyrilene induced a significant increase in mitochondria of periportal hepatocytes in F344 rats. Administration of [3H]-methapyrilene hydrochloride resulted in a pronounced concentration of bound radioactivity in the periportal hepatocytes, with mitochondria being the principal site of intracellular binding. The nuclei of the liver cells were unlabeled. (Author abstract) (8 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

35. FURTHER CHARACTERIZATION OF THE EFFECTS OF 3-METHYLCHOLANTHRENE ADMINISTRATION UPON HEPATIC RIBONUCLEIC ACID POLYMERASE ACTIVITIES.

Liberator PA, Bresnick E
(c/o Bresnick) Vermont Regional Cancer Center, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Chem Biol Interact; 38(1):53-73 1981

The administration of 3-methylcholanthrene (MC) to rats results in a marked increase in the specific activities of hepatic RNA polymerases I and II. In the present study, we were able to show that this increase was not caused by a shift in the ratio of 'free' to 'template-engaged' RNA polymerase. By means of binding studies with [3H]amatoxin, we were unable to demonstrate any increase in the number of RNA polymerase II molecules in liver after MC administration to the rats. RNA polymerase I was purified in excess of 3,000-fold from hepatic nuclei isolated both from control and MC-treated rats. The stimulation in activity was demonstrated at each step in the purification scheme until glycerol sedimentation analysis. Results from cation-exchange chromatography on phosphocellulose indicated that the polycyclic hydrocarbon increased the enzyme activity of RNA polymerase Ib somewhat specifically. Subsequent to glycerol gradient centrifugation, this stimulatory advantage was no longer evident. Reconstitution experiments revealed the presence of a stimulatory component, which was demonstrated in low mol wt fractions from both control and experimental preparations. (Author abstract) (47 Refs)

36. MOLECULAR BASIS FOR INCREASED SYNTHESIS OF ALBUMIN IN RAT LIVER AFTER THIOACETAMIDE ADMINISTRATION.

Chakrabartty PK, Chattopadhyay S K, Schneider WC
(c/o Chattopadhyay), NIH, Building 41, Room A-114, Bethesda, MD, 20205
Cancer Res; 42(2):421-428 1982

Administration of thioacetamide to rats for 4 days has been shown previously to increase the activity of liver messenger RNA (mRNA) and to disproportionately increase the activity of albumin mRNA in the wheat germ translation system. We have explored the possibility that administration of thioacetamide quantitatively alters the transcription of rat liver unique DNA. Nucleic acid hybridization between radioactive rat liver unique DNA and RNA from untreated as well as 4-day thioacetamide-treated rat liver indicates that that normal extent of transcription is not altered by the drug treatment. We also investigated the possibility that thioacetamide treatment increases the level of mRNA in general or of albumin mRNA in particular. Albumin mRNA, which is the most abundantly represented population in rat liver cytoplasmic mRNA, was further enriched by sucrose gradient fractionation of the liver mRNA.

Synthesis of complementary DNA (cDNA) and then use of the strategy of limited hybridization yielded the cDNA corresponding to albumin mRNA. Hybridization of the fractionated cDNA with mRNA from untreated livers as well as from livers with increasing days of treatment shows no change in the level of albumin mRNA. The results indicate that drug treatment induces the augmented synthesis of albumin by disproportionately increasing the translational activity of albumin mRNA. Quantitation of gene dosage by comparison of hybridization kinetics of fractionated cDNA and unique [3H]DNA with total rat cellular DNA indicates that there are not more than two copies of the albumin gene present in the rat genome. (Author abstract) (23 Refs)

37. PREFERENTIAL ATTACK OF MITOCHONDRIAL DNA BY AFLATOXIN B1 DURING HEPATOCARCINOGENESIS.

Niranjan BG, Bhat NK, Avadhani NG
Lab. Biochemistry, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Science; 215(4528):73-75 1982

Administration of the hepatic carcinogen aflatoxin B1 to experimental animals results in covalent binding to liver mitochondrial DNA at concentrations three to four times higher than nuclear DNA. The concentration of carcinogen adducts in mitochondrial DNA remains unchanged even after 24 hr, possibly because of lack of excision repair. Similarly, mitochondrial transcription and translation remain inhibited up to 24 hr suggesting long-term effects of aflatoxin B1 on the mitochondrial genetic system. (Author abstract) (16 Refs)

38. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS AND ELECTRICAL CHARACTERISTICS OF NORMAL LIVER AND HEPATOMA. I. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS IN INDUCED MURINE HEPATOMA.

Sharovskaia IuIu, Mittel'man LA, Smolianinov VV, Chailakhian LM
Res. Lab. Molecular Biology and Bio-organic Chemistry, M. V. Lomonosov State Uni v., Moscow, USSR
Tsitologiia; 23(10):1142-1148 1981

Permeability of the intercellular communications was studied in C3HA mice with o-aminoazotoluene-induced hepatomas. Transmembrane potentials, the input resistance, and distribution of the electric potential measured in hepatoma tissue at different stages of carcinogenesis did not differ from those in normal liver tissue. It was suggested that highly-permeable intercellular communications play a nonspecific role in malignant transformation. (12 Refs) (In RUS)

REVIEWS AND OTHER RELATED STUDIES

39. PRIMARY HEPATIC CARCINOMA.

Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981

Primary hepatic carcinoma (PHC) was reviewed. The following topics were discussed: etiology (cirrhosis, food, infections, parasites, hormones, thorotrast, As, and vinyl chloride), pathologic anatomy (tumors derived from the parenchyma or the mesenchyme), diagnosis (clinical, biological, and morphological), and treatment. (41 Refs) (In SPA)

40. TOXIC AND METABOLIC LIVER INJURY.

Teschke R, Nishimura M, Gellert J
Medizinische Klinik D, Universitat Dusseldorf, Moorenstr. 5, D-4000 Dusseldorf, W. Germany
Leber Magen Darm; 11(5):227-234 1981

Studies on liver damage due to toxic substances and endogenous metabolites are reviewed. Liver cirrhosis due to phenylbutazone, dantrolen, diazepam, isoniazid, alpha-methyldopa, oxyphenisatin, azathioprin, mercaptopurine, methotrexate (MTX), and methyltestosterone was observed. Focal nodular hyperplasia due to oral contraceptives (ethinyl estradiol, mestranol, norethynodrel and norgestrel) was reported in the literature. These oral contraceptives, as well oxymetholone and methyltestosterone were found to induce hepatocellular adenoma. Hepatocellular carcinoma was found in patients treated with MTX, oral contraceptives, oxymetholone and methandrostenolone. (24 Refs) (In GER)

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1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. SMOKING AS RISK FACTOR FOR DIFFERENT FORMS OF CANCER AMONG 26,000 MEN AND WOMEN IN NORWAY. MATCHING OF THE GROUP OF SMOKERS WITH THE CANCER REGISTRY OVER A 12-YEAR PERIOD.

Lund E, Zeiner-Henriksen T
Kreftregisteret, Montebello, Oslo 3, Norway
Tidsskr Nor Laegeforen; 101(34-36):1937-1940 1981

The cancer risk due to smoking was studied among 11,979 men and 13,998 women born between 1895 and 1929 on the basis of data in the Norwegian Cancer Registry for the period 1966-1977. A total of 1,815 cases of cancer were registered for this group during the studied period. Nonsmokers accounted for 22.4% among men and 76.5% among women, ex-smokers for 21.7% and 4.2%, current smokers for 55.4% and 19.1%, and the smoking habits of 0.5% of the men and of 0.2% of the women are unknown. The age-adjusted relative risk (relative to nonsmokers) per 1,000 men was found to be 4.8 for lung cancer and 2.3 for cancer of the urinary bladder and urethra. For women, the relative risk was found to be 1.9 for lung cancer, 1.5 for cancer of the urinary bladder and urethra and 1.3% for cancer of the uterine cervix. The relative risk for all smokers was found to be 1.4 for lip cancer (men), 7.5 for stomach cancer (men), 4.4 for colon cancer (men), 0.9 for larynx cancer, 9.2 (men) and 1.7 (women) for lung cancer, 3.3 for cancer of the uterine cervix, 12.4 for prostate cancer, 3.7 (men) and 1.2 (women) for cancer of the urinary bladder and urethra, 4.8 (men) and 3.4 (women) for lymphoma and leukemia. Significant difference between smokers and nonsmokers was found with respect to laryngeal cancer (men), esophageal cancer (men), cancer of the liver and bile ducts (women) and carcinoma of the uterine cervix as well. The risk of cancer of the upper respiratory passages are higher for pipe smokers than for cigarette smokers, while cigarette smokers had higher risk of lung cancer than pipe smokers. The cancer risk was found to be lower among ex-smokers than current smokers, and it increased with cigarette consumption. (17 Refs) (In NOR)

2. CANCER RISKS IN PEDIATRIC NUCLEAR MEDICINE (MEETING ABSTRACT).

Swanson MA, Hines HH
University of California Davis Medical Center, Sacramento, CA
Clin Nucl Med; 6(9S):448 1981

Because of pediatricians' interest in long term effects of radiation in childhood, the authors have prepared cancer risk estimates for three more commonly ordered pediatric scans and compared them with the spontaneous incidence of the same cancers in the unexposed population. Calculations were based on age, weight and scan dose, assuming an average life expectancy of 70 years. The BEIR III linear-quadratic model was used to estimate 30 year leukemia and bone cancer risk and the BEIR III linear model for the lifetime risk of hepatic neoplasms. Absorbed dose estimates were taken from the literature for cancer risk calculations. (no Refs)

3. MEMBRANOUS OBSTRUCTION OF THE INFERIOR VENA CAVA: ETIOLOGY AND RELATION TO HEPATOCELLULAR CARCINOMA.

Okuda K
Dept. Medicine, Chiba Univ. Sch. Medicine, Chiba, Japan
Gastroenterology; 82(2):376-379 1982

Membranous obstruction of the inferior vena cava (MOVC) and relations to hepatocellular carcinoma (HCC) are reviewed. MOVC appears to occur more frequently in developing areas of the world. The relationship between MOVC and (HCC) is poorly understood and may represent multifactorial oncogenetic processes. In a recently reported series, incidence of 22.2% hepatitis B surface antigen (HBsAg) in patients with MOVC in South Africa was higher than in healthy persons (8.7%), but lower than that in patients with HCC (33.7%). This may suggest that hepatitis B virus infection is not the only factor in hepatocarcinogenesis, and that high incidence of HCC patients with MOVC may be due to the long duration of chronic liver damage in MOVC. HCC has been described also with a wide variety of chronic liver diseases including hemochromatosis, alpha1-antitrypsin deficiency, schistosomiasis, clonorchiasis, and Thorotrast liver disease. Since the incidence of HBsAg carrier state is much higher in blacks of South Africa, but the incidence of HCC is similar to that of Japan, perhaps blacks are exposed to lower concentrations of chemical carcinogens. (30 Refs)

4. AN EPIDEMIOLOGICAL STUDY ON THE POSSIBLE ASSOCIATION BETWEEN INTAKE OF BROILED FISH AND CANCER (MEETING ABSTRACT).

Ikeda M, Yoshimoto K, Yoshimura T, Kono S, Kato H, Kuratsune M
Department of Public Health, Fac. of Medicine, Fukuoka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Yr ago, the Radiation Effects Research Foundation investigated 7,553 subjects for dietary habits such as frequency of consumption of broiled fish, milk, and others. Therefore, the possible association between these habits and their cancer deaths seen during 11 yr was investigated by the linear multiple stepwise regression analysis. Frequent consumption of broiled fish was significantly positively associated with deaths from all sites of cancer and those from gastric cancer. Liver cancer was also associated with this habit but with no statistical significance. (no Refs)

5. RELATION BETWEEN CANCER DEATH AND FOODS CONSUMPTION --- SEVEN SITES IN DIGESTIVE ORGANS (MEETING ABSTRACT).

Nagai M, Hara N, Sakata K, Hashimoto T, Yanagawa H
Department of Public Health, Jichi Medical School, Tochigi, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The areal difference of the mortality from cancer of 7 sites of digestive organs and consumption of foods in 46 prefectures and their capital cities were observed and analyzed by correlation and factor analysis. The standardized mortality ratios (SMR) for male were calculated over 10 yr (1969-'78). The variables on food consumption were selected from two surveys conducted by Prime Minister's Office. The foods statistically suspected as risk factors are: 1) pork, oil and shochu for esophagus cancer; 2) fresh fishes, salted fishes, vegetables and alcoholic drinks for stomach cancer; 3) alcoholic drinks, salted fishes, vegetables, bread, milk, butter, margarine, ketchup, beer and fresh fishes for colon cancer; 4) fresh fishes, salted fishes, salt and sake (2nd class) for rectal cancer; 5) pork, sake (2nd) and green tea for bile ducts cancer; 6) salted fishes, vegetables, alcoholic drinks, oil and fresh fishes for pancreas cancer; 7) beef, chicken, egg and vinegar for liver cancer. (no Refs)

6. SPATIAL PATTERN OF PRIMARY LIVER CANCER COMPARED TO THAT OF OESOPHAGEAL CANCER IN GOLDMINERS FROM TRANSKEI, 1964-1979.

McGlashan ND, Harington JS, Bradshaw E
(c/o Harington) Cancer Res. Dept., National Cancer Association, P.O. Box 2000, Johannesburg 2000, South Africa
S Afr J Sci; 77(10):471-473 1981

The spatial pattern of primary liver cancer was compared to that of esophageal cancer in goldminers from Transkei; detailed geographic analysis of places of recruitment for cases of esophageal cancer revealed a significant similarity with the spatial pattern of Transkei residents, both male and female, who had not been absent while migrant laborers. (5 Refs)

7. NATIONWIDE SURVEY OF MAJOR LIVER DISEASES IN THAILAND ANALYSIS OF 3,305 BIOPSIES AS TO YEAR-END 1978.

Bunyaratvej S, Meenakanit V, Tantachamrun T, Srinawat P, Susilaworn P, Chongchitnan N
Dept. Pathology, Faculty Medicine, Ramathibodi Hosp., Mahidol Univ., Bangkok 4, Thailand
J Med Assoc Thai; 64(9):432-439 1981

Liver cancer, cirrhoses, and inflammatory diseases were surveyed in different regions of Thailand. Liver cancer was more prevalent in the northeast (73.4% of all liver diseases) and in the north (Khonkaen) (42.5%) than in the south (36.8) and central (26.0%) areas. Hepatocellular carcinoma (HPC) was the most common liver cancer in the north (29.5), and cholangiocarcinoma (CC) was most frequently found in the northeast (46.2%). Metastatic carcinoma occurred more in the south (9.4%). HPC affected men 5x more than women, and men also were affected with CC twice as often as women. HPC rate reached a peak in the fifth decade and descended thereafter. Acute viral hepatitis comprised 2.1-4.3% of liver diseases in the different areas, chronic hepatitis 2.1-8.5%. While a high association between CC and opisthorchiasis has been reported, no significant association of viral hepatitis to opisthorchiasis associated CC could be found. Parasitic infections associated with the consumption of raw fish and high levels of nitrates and nitrites in food and surface waterss are discussed as factors in the regional patterns of liver disease. (29 Refs)

8. USE OF MULTIPLE TUMOUR MARKERS IN THE SCREENING FOR EARLY PRIMARY HEPATOCELLULAR CARCINOMA IN THE POPULATION IN SINGAPORE (MEETING ABSTRACT).

Oon CJ, Chio LF, Singh R, Chan L, Lim GK, Yo SL
Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316, Singapore
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

From 1979-1981 an ongoing prospective study was done on high-risk groups of the population in Singapore to determine the incidence of the primary hepatocellular carcinoma (PHC) in the various at risk groups. The groups studied were: 1000 normal males over 40 yr, 160 immediate PHC family members, 80 cirrhosis, 60 chronic hepatitis B carriers, 250 women on oral contraceptives and 50 males on androgen replacement therapy. Tumor markers used were Alphafetoprotein (AFP) (CIE), alpha1 antitrypsin (ATT), alpha1acidglycoprotein I, gammaglutamyl transpeptidase (GGT), and isocitrate dehydrogenase. Three of 1000 normal male population, (0.3%), 4/160 family PHC members (2.5%), 30/80 (38%) cirrhosis, 6/60 (10%) chronic hepatitis B carriers and 4/150 (1.6%) women on estrogen progesterone pills developed PHC. Hepatomegaly, (not due to a medical cause) was caused by PHC in 45/80 (56%) of patients. No male patients on normal androgen replacement therapy developed PHC after 3 yr follow up. AFP, ATT and GGT remain the most useful detector for PHC. Specific isoenzymes of ATT and GGT may be more useful in differentiating PHC from other conditions. Raised ATT levels in pill takers returned to normal on discontinuation. Only 10% of detectible tumors were resectible. All tumors detectible preclinically were 10 cm diameter (+/-) 2 cm. Three of 3 (100%) of these patients are alive at 1 yr follow up. (no Refs)

9. INCIDENCE OF MALIGNANT NEOPLASMS OF DIGESTIVE ORGANS.

Zemla B, Kolosza Z, Czech J, Jamrozik W
Instytut Onkologii, ul. Wybrzeze Armii Czerwonej 15, 44-101 Gliwice, Poland
Wiad Lek; 34(13):1077-1083 1981

Epidemiological data on the incidence of malignant neoplasms of the digestive organs in the population of Zabrze and its suburbs between 1965-1975 are presented. Malignant neoplasms of digestive organs were diagnosed in 199 men and 205 women. Esophageal tumors were diagnosed in 6 men and 4 women, gastric tumors in 130 men and 71 women, colon tumors in 14 men and 41 women, rectal tumors in 11 men and 23 women, hepatic tumors in 11 men and 20 women, gallbladder tumors in 5 men and 23 women, and tumors of the pancreas, peritoneum and undetermined localizations in 20 men and 27 women. The standardized incidences per 100,000 population were 1.64 for esophageal tumors, 32.96 for gastric tumors, 3.45 for colon tumors, 2.86 for rectal tumors, 2.81 for hepatic tumors and 50.96 for all localizations in men. The corresponding incidences in women were 0.30, 11.10, 6.54, 3.60, 3.07 and 32.03. The incidence of malignant tumors of the digestive organs, especially of the stomach, was significantly lower in the autochthonous populations of districts supplied with water of relatively high hardness, ie, with high levels of magnesium salts, chlorides and sulfates, than in the immigrant population. (8 Refs) (In POL)

10. NEOPLASIAS OF THE LIVER IN CHILDREN.

Coronado Perez H, Angulo Hernandez O
Servicio de Patologia, Hospital de Especialidades, Centro Medico La Raza, Mexico D.F., Mexico
Bol Med Hosp Infant Mex; 38(5):723-740 1981

Results were reported of a retrospective study of hepatic tumors in 27 children; 16 of the children had hepatoblastomas (HB: 7 epithelial and 9 mixed), 2 had hepatocellular carcinomas (HC), 4 had mesenchymal hamartomas, 2 had infantile type hemangioendotheliomas (HE), 2 had embryonal rhabdomyosarcomas (RS) of the intrahepatic bile duct, and 1 had a multiple hamartoma of the bile duct. The HB patients (10 male, 6 female; 10 mo to 9 yr old, but 13 greater than 2 yr old) had vague symptoms and increased alkaline phosphatase (AP: 300-1,800 units); only two had jaundice. Virilization was not observed. Ten of the HB were located in the right lobe of the liver (as single masses 6-15 cm in diameter), and 6 were located in both lobes (as multiple nodules in some cases). Only three patients had lobectomies, followed by chemotherapy (CT); times of survival for these patients were 13 mo, 6 yr, and 4 yr. At the time of death, all had pulmonary metastases (ME). Nine patients were administered radiotherapy and CT as palliative measures, and four because of advanced disease, received no therapy; survival times were 1 wk to 6 yr (av, 5 mo). Two patients (7-yr-old boy and 15-yr-old girl) had palpable HC and increased AP (196 and 548 units, respectively); right and left lobectomies were performed. One of these patients was well for 2 yr; the other received 5-fluorouracil and was well for 1 yr. Two girls (2-3 mo old) had laparotomies, which revealed multiple nodules of HE. One died after surgery; the other received prednisone, was asymptomatic for 2 yr, and then was lost. Diagnosis of RS was established at autopsy in two patients (9-yr-old boy and 21-mo-ld girl). (25 Refs) (In SPA)

11. HEPATOBLASTOMA IN ADULTS.

Babaryka I, Von Bouquoy F
Pathologisches Institut, Stadtisches Krankenhaus Schwabing, Kolner Platz 1, D-8000 Munchen 40, W. Germany
Leber Magen Darm; 11(6):283-286 1981

Occurrence of hepatoblastoma in a 73-yr-old woman is reported. The patient presented with obstructive jaundice. During laparotomy was performed 5 wk later, massive empyema of the gall bladder and a firm, infiltrating tumor of the liver portal were found. The patient suffered cardiopulmonary arrest immediately after surgery and died the following day after massive hemorrhage from the mouth and nose. Autopsy revealed a 9 x 8 x 8 cm tumor located primarily in the right lobe of the liver. Cause of death was a hemorrhagic erosion of the stomach. Histologic examination showed the tumor to be composed of epithelial elements (fetal hepatic cells) and mesenchymal elements (spindle-shaped, fibroblast-like cells and focal osteoid tissue), mesenchymal elements being predominant. No evidence of metastasis was found. Review of literature indicated that hepatoblastoma occurs only rarely in adults. Etiology and pathogenesis are uncertain, but hepatoblastoma apparently originates from multipotent blastema capable of epithelial or mesenchymal differentiation. Related factors include inflammation, drugs or poisons, and use of oral contraceptives. Metastases are frequent. Hepatoma usually causes death within 6 mo in children, but the disease progresses slowly in adults. (25 Refs) (In GER)

TUMOR INDUCTION IN ANIMALS

12. INDUCTION, CHARACTERIZATION AND ISOLATION OF PRENEOPLASTIC HEPATOCYTES AFTER COMBINED TREATMENT WITH 2-ACETYLAMINOFLUORENE AND FERRIC NITRILOTRIACETATE.

Bibbiani C, Malvaldi G
Istituto di Patologia Generale, Universita di Pisa, Pisa, Italy
Boll Soc Ital Biol Sper; 57(16):1722-1726 1981

Male rats (Sprague-Dawley, 80-90 g) were administered for 8 wk ferric nitrilotriacetate (Fe-NTA; 0.5 ml/100 g/day ip) and 2-acetaminofluorene (2-AAF; 300 mg/kg standard diet without antioxidants). Control animals were administered the same dose of Fe-NTA. One wk after the end of treatment, liver was perfused in situ with Hanks soln without Ca. Two liver tissue specimens were removed for histological and histochemical testing. Liver perfusion was followed with collagenase, and at the end of perfusion, hepatocytes were removed by bland mechanical treatment. Part of the suspension was used to prepare smears and for biochemical testing, the rest was further purified. Partial separation of different cells was accomplished by isopycnic gradient separation. Combined administration of Fe-NTA and 2-AAF induced formation of small nodules or areas made of HC without iron that can be easily identified due to the absence of pigment. Gamma glutamyltranspeptidase activity was demonstrated in areas without iron, while glucose-6-phosphatase activity disappeared. (15 Refs) (In ITA)

MODIFICATION OF HEPATOCARCINOGENESIS

13. METHAPYRILENE EFFECTS ON INITIATION AND PROMOTION OF GAMMA-GLUTAMYL-TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER.

Couri D, Wilt SR, Milks MM
Div. Toxicology, Dept. Pharmacology, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210
Res Commun Chem Pathol Pharmacol; 35(1):51-61 1982

The initiating and promoting effects of methapyrilene were evaluated using the hepatic enzyme-altered foci bioassay. Male Sprague-Dawley rats were partially hepatectomized and 24 hr later were administered either methapyrilene or nitrosodiethylamine by oral gavage. Subsequently, the animals were promoted with 500 ppm phenobarbital or 200 ppm methapyrilene in drinking water for 8 wk. Fresh frozen sections of liver were then stained and scored for gamma-glutamyl-transpeptidase (GGT)-positive foci. Methapyrilene, when tested as the nominal initiator at a single dose of 50 mg/kg or at two doses of 130 mg/kg and promoted by phenobarbital, did not induce foci above background levels. However, when substituted for phenobarbital as the promoting agent following nitrosodiethylamine initiation, methapyrilene enhanced enzyme-altered foci formation to an equal or greater extent than did the promoter phenobarbital. These results suggest that the carcinogenic effects of methapyrilene may be related to its ability to enhance hepatic tumorigenesis. (Author abstract) (19 Refs)

14. PROMOTION BY POLYCHLORINATED BIPHENYLS OF ENZYME-ALTERED FOCI IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U.S. Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45267
Cancer Lett; 15(2):185-190 1982

The number of gamma-glutamyltranspeptidase (GGTase)-positive foci was examined in livers of partially hepatectomized male Sprague-Dawley rats given an initiating dose of diethylnitrosamine (DENA: 0.3 millimole/kg body wt, po) followed 7, 28, or 49 days later by one to three doses of Aroclor 1254 (500 mg/kg, ip). Rats were killed 21 days after the last dose of Aroclor. Incidence of GGTase-positive foci increased from a mean of 0.70 foci/square cm (cm2) liver in solvent (tricaprylin)-treated, partially-hepatectomized, DENA-initiated controls to 2.28 foci/cm2 in animals given a single dose of Aroclor 1254. Maximum enhancement was obtained after two doses, which resulted in 3.47 foci/cm2. Up to three doses of Aroclor did not increase the incidence of GGTase-positive foci in partially-hepatectomized animals that had not received DENA. Aroclor

1254 appears suitable as an inexpensive promotor in a short-term initiation/promotion assay for chemical carcinogens. (20 Refs)

15. EFFECT OF PHENOBARBITAL, POLYCHLORINATED BIPHENYL AND SODIUM SACCHARIN ON HEPATIC AND RENAL CARCINOGENESIS IN UNILATERALLY NEPHRECTOMIZED RATS GIVEN N-ETHYL-N-HYDROXYETHYLNITROSAMINE ORALLY.

Hirose M, Shirai T, Tsuda H, Fukushima S, Ogiso T, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(12):1299-1302 1981

The effects of phenobarbital (PB), polychlorinated biphenyl (PCB) and sodium saccharin (SS) on hepatic and renal carcinogenesis induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN) were examined in male F344 rats. The rats were given 0.1% EHEN in their drinking water for 2 wk and then diet containing 0.05% PB, 0.05% PCB or 5% SS for 32 wk. In wk 3, the right kidney was removed to promote renal neoplasia. The incidence of hepatocellular carcinoma was much higher in rats given PB or PCB than in controls given EHEN alone. PB administration significantly decreased the av number of renal-cell tumors per un it area and SS reduced the numbers of early neoplastic nodules. Treatment with PCB had no effect on renal carcinogenesis. These results indicate that chemicals may have either a promotive or inhibitory effect depending on the organ. (Author abstract) (25 Refs)

16. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYL-ACETAMIDE INDUCED RAT LIVER LESIONS (MEETING ABSTRACT).

Tanaka T, Mori H, Nishikawa A, Takahashi M
Department of Pathology, Medical Gifu University, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Comparison of enhancing effects of phenobarbital (PB) and barbital (B) in hepatotumorigenesis was examined by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats of 2 mo old were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. Remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% B diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin or iron stain specimen/cm2 of the liver space at 16 wk of Group I remarkably decreased compared to that at termination of FAA feeding. However, the number of Group II or III was similarly maintained at 8 and 16 wk and the number at 16 wk of both groups was significantly higher than that of Group I. These data show that B like PB could be an enhancer in hepatotumorigenesis. (no Refs)

17. HEPATOCARCINOGENICITY OF DIETHYLSTILBESTROL (DES) IN RATS (MEETING ABSTRACT).

Kamiya K, Seyama T, Kodama Y, Numoto M, Yokoro K
Department of Pathology, Hiroshima University, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Despite the demonstration of carcinogenicity of DES in estrogen-susceptible tissues of some animal species, little is known about its carcinogenic effect in the liver. Castrated W/Fu rats treated with DES alone developed tumors of the liver (HT) in 30% of animals. By a combined treatment of DES and N-nitrosobutylurea (NBU) which is not hepatocarcinogen itself, HT incidence is much increased in several rat strains. In this system, androgen had no promotive effect in HT induction and the incidence correlated well with the dosage of DES. While castration prevents N-2-fluorenylacetamide (2-FAA) induced hepatocarcinogenesis, a combined treatment of 2-FAA and DES in castrated rats remarkably increased the incidence and tumor size of HT and shortened the latent period, suggesting the promotive effect of DES on the growth of transformed cells initiated by 2-FAA. Those results indicate that DES is a complete carcinogen with activities stronger in promotion than in initiation. (no Refs)

18. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS; SUMMATION VERSUS PROMOTION EFFECTS (MEETING ABSTRACT).

Katayama S, Ohmori T, Williams GM

Department of Pathology, Osaka University Medical School, Osaka, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The enhancement of the effects of a carcinogen by a subsequently administered chemical is routinely regarded as evidence of promotion. On the other hand, as an extension of summation of multiple irreversible alterations produced by the total dose of a carcinogen, Nakahara and others have shown that sequential administration of two different carcinogens will produce a summation effect. Thus, the operational definition of a promoter based solely upon its enhancing effect in a protocol of sequential administration becomes questionable. To examine this problem, we undertook a comparison of the effects of phenobarbital (PB) versus diethylnitrosoamine (DEN) when each was given after 2-acetylaminofluorene (AAF). The effects of PB and DEN were comparable, however DEN exerted a greater enhancing effect on the oncogenic outcome of AAF exposure than PB. (no Refs)

19. ENHANCEMENT OF AFLATOXIN B1 INDUCED LIVER CARCINOGENESIS BY PORTAL DIVERSION IN THE RAT.

Franco D, Morin J, Szekely AM, Bismuth H

Departement de Recherche Chirurgicale, Universite Paris-Sud, Hopital Paul-Brousse, 14, Avenue Paul-Vaillant-Couturier, 94800 Villejuif, Cedex, France

Biomedicine [Express]; 35(5):162-165 1981

Conflicting results have been reported on the influence of portacaval anastomosis on liver carcinogenesis. The purpose of this investigation was a study the effect of portal diversion on liver carcinogenesis induced in the rat by a potent chemical liver carcinogen, Aflatoxin B1 (AFB1). Liver tumors appeared earlier and were significantly bigger in rats with shunts than in sham-operated controls. Portal diversion also induced in rats fed AFB1 a splenic atrophy with nearly complete disappearance of Malpighian corpuscles suggesting a profound immunodepression. This might be responsible for the enhancement of liver cancer by portacaval anastomosis in the rats fed AFB1. Thus, the influence of portal diversion on liver cancers appears to be multifactorial. (Author abstract) (12 Refs)

20. HEPATOTOXIC RESPONSE OF GERMFREE RATS TO DIMETHYLNITROSAMINE (DMN) INTUBATED (MEETING ABSTRACT).

Sumi Y, Miyakawa M
Nagoya University School of Medicine, Nagoya, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

This study was designed to know whether or not gut microflora is involved in the process of the formation of hepatic lesion by DMN. Thirty-eight germfree and 60 conventional Wistar male rats were employed. DMN was intubated with stomach tube at respective doses of 8, 9 and 10 mg/kg body wt. Forth-eight hr after the intubation, a severe liver necrosis accompanied with hemorrhage was produced at each dose in germfree rats while no such severe liver necrosis was found at each dose in conventional rats, and this result was consistent with that of tests for SGOT and SPGT, indicating that germfree status might play a part in the augmentation of hepatic lesion by DMN. It might be concerned with difference in DMN metabolism or in immunobiological background. (no Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

21. STEREOSELECTIVE METABOLISM OF THE OPTICAL ISOMERS OF TRANS-1,2-DIHYDROXY-1,2-DIHYDROPHENANTHRENE TO BAY-REGION DIOL EPOXIDES BY RAT LIVER MICROSOMES.

Vyas KP, Thakker DR, Levin W, Yagi H, Conney AH, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism and Diseases, NIH, Bethesda, MD, 20205
Chem Biol Interact; 38(2):203-213 1982

Enantiomerically pure isomers of trans-1,2-dihydroxy-1,2-dihydrophenanthrene have been obtained by chromatographic separation of their diastereomeric bis esters with (-)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid. Liver microsomes from control rats, as well as rats treated with phenobarbital or 3-methylcholanthrene, metabolize these dihydrodiols to a pair of diastereomercially related bay-region 1,2-diol-3,4-epoxides in which the benzylic hydroxyl group and the epoxide oxygen are either cis (isomer-1) or trans (isomer-2) to each other. In general, diol epoxide-1 was the major metabolite of the (+)-(1S,2S)-dihydrodiol, whereas diol epoxide-2 was the major metabolite of the (-)-(1R-2R)-dihydrodiol. The extent of this stereoselectivity is dependent on the source of the microsomes and is greatest for liver microsomes from 3-methylcholanthrene-treated rats; the ratio of diol epoxide-1 relative to diol epoxide-2 was 5.6 : 1 with the (+)-enantiomer as substrate and 1 : 5.5 with the (-)-enantiomer as substrate. For a given microsomal preparation, rates of metabolism were independent of the enantiomer composition of the substrate. Relative to microsomes from control animals, treatment of rats with 3-methylcholanthrene enhanced rates of metabolism by about 40%, whereas treatment with phenobarbital decreased rates to a similar extent when the amounts of metabolites formed per nanomole of cytochrome P-450 were compared. The failure of treatment by 3-methylcholanthrene to enhance markedly the rate of metabolism of a polycyclic aromatic hydrocarbon substrate is unusual. (Author abstract) (16 Refs)

22. EFFECTS OF 3-METHYLCHOLANTHRENE, BETA-NAPHTHOFLAVONE, AND PHENOBARBITAL ON THE 3-METHYLCHOLANTHRENE-INDUCIBLE ISOZYME OF CYTOCHROME P-450 WITHIN CENTRILOBULAR, MIDZONAL, AND PERIPORTAL HEPATOCYTES.

Baron J, Redick JA, Guengerich FP
Dept. Pharmacology, Toxicology Center, Coll. Medicine, Univ. Iowa, Iowa City, IA, 52242
J Biol Chem; 257(2):953-957 1982

Rabbit antiserum produced against cytochrome P-450 MC-B, the major isozyme of cytochrome P-450 isolated from hepatic microsomes of 3-methylcholanthrene-pretreated rats, was utilized in unlabeled antibody peroxidase-antiperoxidase and indirect fluorescent antibody staining techniques to investigate the effects of 3-methylcholanthrene, beta-naphthoflavone, and phenobarbital on the hemeprotein within centrilobular, midzonal, and periportal hepatocytes in livers of male rats. In livers of untreated and vehicle-pretreated rats, midzonal and periportal hepatocytes were found to bind the anti-cytochrome P-450 MC-B to equal extents while centrilobular hepatocytes bound approximately 25% more antibody. Pretreatment of rats with phenobarbital did not result in alterations in either the intensity or pattern of immunohistochemical staining for cytochrome P-450 MC-B within the liver lobule. In livers of rats which had been pretreated with 3-methylcholanthrene, microfluorometric analyses revealed that the extent of anti-cytochrome P-450 MC-B binding increased by approximately 215% within both the midzonal and periportal regions of the lobule and by approximately 150% within centrilobular regions. Pretreatment of rats with beta-naphthoflavone resulted in alterations in the hemeprotein which were similar to those produced by 3-methylcholanthrene. Thus, after rats had been pretreated with either 3-methylcholanthrene or beta-naphthoflavone, the pattern of intralobular distribution of cytochrome P-450 MC-B was altered so that the antibody bound to approximately equal extents to hepatocytes within the three regions of the lobule. These results demonstrate that 3-methylcholanthrene and beta-naphthoflavone exert similar inductive effects on cytochrome P-450 MC-B within the liver lobule, with the least degree of induction of the hemeprotein being produced within centrilobular hepatocytes. (Author abstract) (42 Refs)

23. METABOLISM OF DICHLOROBIPHENYLS BY HIGHLY PURIFIED ISOZYMES OF RAT LIVER CYTOCHROME P-450.

Kaminsky LS, Kennedy MW, Adams SM, Guengerich FP
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Biochemistry; 20(26):7379-7384 1981

Hepatic mixed-function oxidase metabolism of the ubiquitous pollutant polychlorinated biphenyls (PCBs) is implicated in their toxification and detoxification. We used dichlorobiphenyls (DCBs) as models to investigate the effect of the chloro substituent sites on this metabolism experimentally and by molecular orbital calculations. Reconstituted, purified cytochrome P-450 PB-B and BNF-B, the major terminal oxidase isozymes of this system, from phenobarbital (PB)- and beta-naphthoflavone (BNF)-induced rats were used to investigate this metabolism. Both isozymes are also induced by PCBs. High-performance liquid chromatography (HPLC) was used to detect, quantify, and isolate metabolites. Metabolite structures were identified by mass spectrometry, dechlorination to identifiable hydroxybiphenyls, and HPLC retention times. All DCBs yielded 3-and 4- but no 2-monohydroxylated metabolites (3,3'-DCB also yielded a dihydroxy metabolite). Di-o-chloro-substituted DCBs were metabolized primarily by cytochrome P-450 PB-B, mono-o-chloro substituted DCBs by both isozymes approx equivalently, and DCBs without o-chloro substituents by BNF-B primarily. Thus PB-B preferentially metabolizes noncoplanar DCBs and BNF-B coplanar DCBs. The cytochrome isozymes exhibited differing regioselectivities for DCB metabolism-PB-B hydroxylated unchlorinated phenyl rings and BNF-B chlorinated rings. Incorporation of epoxide hydrolase yielded DCB dihydrodiols, and hydroxy metabolite patterns were consistent with those calculated from ring-opened arene oxide intermediates. Thus the rates and regioselectivities of metabolism and thus possibly the toxicity and carcinogenicity of DCBs are dependent on the cytochrome P-450 isozymes induced. (Author abstract) (42 Refs)

24. METABOLISM OF 2-ACETYLAMINOFLUORENE IN PRIMARY RAT HEPATOCYTE CULTURES.

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J Toxicol Environ Health; 7(1):93-106 1981

The kinetics of 2-acetylaminofluorene (AAF) metabolism are investigated at various doses and with varying cell culture conditions. Primary cultures of 2 x 10(6) Sprague-Dawley rat hepatocytes metabolized all of a dose of 137 ng of 13.7 ug AAF during 12-24 hr of incubation. At higher concentrations of AAF per 2 x 1(6) cells, the rate of metabolism diminished and water-soluble metabolites appeared at 70% the rate at lower doses. Presumptive covalently bound AAF residues reached a max of 5% of the adminstered 137 ng per 2 x 10(6) M cells. The rate of appearance of water-soluble AAF metabolites was stimulated by the addition of hormones to the culture medium, correlating with the enhanced cytochrome P-450 levels in hormone-treated cells. With 10(-4) M SKF 525A, the metabolism of AAF was diminished 50%; with 10(-3) M, it was eliminated. With 40 ug AAF per 2 x 10(6) cells, 31% of AAF was recovered as water-soluble products after 24 hr. The cells could then metabolize a subsequent 40-ug dose at an undiminished rate. Thus, primary rat hepatocyte cultures constitute an in vitro model for the quantitative study of the cellular disposition of a chemical carcinogen in its presumptive target cell. (43 Refs)

25. INDUCTION OF DRUG-METABOLIZING ENZYMES IN THE RAT LIVER BY 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE.

Hino O, Nemoto N, Nagao M, Kosugi A, Kitagawa T
Dept. Pathology, Cancer Inst., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Cancer Lett; 15(2):131-136 1982

The hepatic drug metabolizing system was examined in male Donryu rats fed a normal diet or a diet containing 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB: 1-600 ppm) for 1 or 3 wk. Microsomal cytochrome P-450 content was not affected after 1 wk of 3'-Me-DAB administration but was significantly higher after 3 wk of treatment with 10, 20, or 600 ppm of the carcinogen. Liver S-9 fraction from rats treated with 3'-Me-DAB (20 or 300 ppm, 3 wk) produced a significant, dose-dependent increase in number of 3-methylcholanthrene-induced revertants in the Ames test; when 3-amino-1-methyl-5H-pyrido[4,3-b]indole was used as the mutagen, a significant increase in the number of revertants was induced by S-9 from rats treated with the higher dose. The results indicate that dietary 3'-Me-DAB induces cytochrome P-450 in the liver and that the increase in drug metabolizing capacity can be detected efficiently by the Ames Salmonella test. (25 Refs)

26. TISSUE-SPECIFICITY OF N-NITROSODIBUTYLAMINE METABOLISM IN SPRAGUE-DAWLEY RATS.

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Dept. Toxicology, Univ. Uppsala, Box 573, S-751 23 Uppsala, Sweden
Chem Biol Interact; 38(2):231-242 1982

The distribution and metabolism of N-[14C]nitrosodibutylamine were studied in Sprague-Dawley rats. The results indicated that in addition to the liver, metabolism of the substance occurred in the nasal mucosa, the lung and the esophagus. Metyrapone and diethyldithiocarbamate reduced the production of 14CO2 from N-[14C]nitrosodibutylamine by all these tissues. There was no indication of metabolic capacity in the urinary bladder or the kidney. The results fit with the assumption that tumors of the urinary tract are induced by metabolites reaching these tissues via the urine. Besides the liver, the esophagus and the lung are target tissues for the carcinogenicity of N-nitrosodibutylamine in Sprague-Dawley rats and in these tissues the local formation of reactive metabolites may play a role in the pathogenesis of N-nitrosodibutylamine-induced lesions. (Author abstract) (21 Refs)

27. WITHDRAWAL TIME REQUIRED FOR CLEARANCE OF AFLATOXINS FROM PIG TISSUES.

Furtado RM, Pearson AM, Hogberg MG, Miller ER, Gray JI, Aust SD
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
J Agric Food Chem; 30(1):101-106 1982

Pigs were maintained on aflatoxin-spiked diets for 42 days and analyzed for tissue clearance of toxins. Pigs were found to rapidly metabolize and clear their tissues of aflatoxins once placed on an uncontaminated diet. This supports the suggestion that the risk from eating liver or meat of animals fed an aflatoxin-contaminated diet are negligible. (31 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

28. SELECTING BINDING AND COMPLEMENT-MEDIATED LYSIS OF HUMAN HEPATOMA CELLS (PLC/PRF/5) IN CULTURE BY MONOCLONAL ANTIBODIES TO HEPATITIS B SURFACE ANTIGEN.

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Proc Natl Acad Sci USA; 79(2):650-654 1982

High-affinity 125I-labeled monoclonal antibodies to hepatitis B virus surface antigen (HBsAg) bind to a human hepatocellular carcinoma cell line, PLC/PRF/5, which synthesizes and secretes HBsAg. These monoclonal antibodies of the IgG1, IgG2a, and IgM isotypes are directed against different antigenic determinants on HBsAg and, in the presence of complement, both anti-HBs IgG2a and IgM, but not anti-HBs IgG1, lyse PLC/PFR/5 cells in culture. Although there is a low level of anti-HBs binding (especially with anti-HBs IgM) to human hepatoma cell lines which do not synthesize HBsAg (SK-Hep 1 and Mahlavu cells), this interaction does not lead to complement-mediated cell lysis and is thought to be nonspecific. Minimal binding of 125I-labeled anti-influenza HA antigen

IgM binding to PLC/PRF/5 cells was also detected, but this likewise did not lead to complement-mediated cell lysis. These results indicate that a human hepatocellular carcinoma cell line, persistently infected with hepatitis B virus, can be recognized and lysed by monoclonal antibodies directed against specific determinants of HBsAg. Monoclonal antibodies to this viral envelope protein may prove to be useful immunodiagnostic and immunotherapeutic agents when such viral epitopes are expressed on the surface of infected cells. (Author abstract) (33 Refs)

29. INDUCTION OF HBSAG FROM HUMAN HEPATOMA CELL LINE (MEETING ABSTRACT).

Watanabe T, Nakamura T, Kumagai N, Inagaki Y, Tsuchimoto K, Morizane T, Tsuchiya M
Department of Internal Medicine, Keio University, Tokyo, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Human hepatoma cell line HCC-M was derived from 34-yr-old Japanese male patient. Serological test for HBsAg was positive but HBeAg was negative. HCC-M did not secrete HBsAg into the culture medium, determined by radioimmunoassay (RIA). By immunofluorescent method, HBsAg was not found in the cytoplasm, nor on the surface of HCC-M. However, when HCC-M was treated with 5-iodo-2'-deoxyuridine (IUDR) for 48 hr, HBsAg was detected by RIA in the supernatant of culture medium. Moreover, a virus-like particle which was not detected in HCC-M was observed by electron microscopy in HCC-M treated with IUDR. These results suggest that some factors interfere with expression of HBsAg in HCC-M. (no Refs)

30. THE EFFECT OF CHRONIC HABITUAL ALCOHOL INTAKE ON THE DEVELOPMENT OF LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: RELATION TO HEPATITIS B SURFACE ANTIGEN CARRIAGE.

Ohnishi K, Iida S, Iwama S, Goto N, Nomura F, Takashi M, Mishima A, Kono K, Kimura K, Musha H, Kotota K, Okuda K
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Cancer; 49(4):672-677 1982

To study the effects of habitual alcohol intake on the latency period for the development of liver cirrhosis and hepatocellular carcinoma (HCC), 158 patients with cirrhosis and 79 with HCC were analyzed with respect to age at the time of diagnosis. They were classified into four groups based on hepatitis B surface antigen (HBsAg) in serum, and the history of intake of more than one small bottle of Japanese 'sake' or an equivalent per day for more than 10 yr. The av age of HBsAg positive male cirrhotics with a drinking habit ($n = 10$) was 38.8 yr, 10.5 yr younger than that of those without a drinking habit ($n = 8$) (p less than 0.05). The av age of HBsAg negative cirrhotics with a drinking habit ($n = 97$) was 47.9 yr, 8 yr younger than that of those not drinking ($n = 36$) (p less than 0.001). There was no significant difference in the laboratory data between these groups. The av age of the HBsAg positive HCC patients with a drinking habit ($n = 20$) was 48.9 yr, 9 yr younger than that of those without a drinking habit ($n = 12$) (p less than 0.05). The av age of HBsAg negative male HCC cases with habitual intake of more than 126 ml of ethanol per day was 51.0 yr ($n = 8$), 10 yr younger than that of nondrinking male HCC cases ($n = 11$) (p less than 0.05). These data suggest that habitual alcohol intake may promote the development of liver cirrhosis and HCC, especially in HBsAg carriers. (Author abstract) (29 Refs)

31. HEPATITIS B ANTIGEN IN THE LIVER IN HEPATOCELLULAR CARCINOMA IN SHIKOKU, JAPAN.

Akagi G, Furuya K, Otsuka H
2nd Dept. Pathology, Sch. Medicine, Kuramoto-cho 3-18-15, Tokushima 770, Japan
Cancer; 49(4):678-682 1982

An analysis of 105 autopsy cases (77 male, 28 female) of hepatocellular carcinoma (HCC) showed that 90 cases (85.7%) were associated with liver cirrhosis, of which 75 cases (83.3%) were of the macronodular type. Hepatitis B surface antigen (HBsAg) was detected with orcein stain in the hepatic tissue in 58 cases (55.2%). The incidence of HBsAg in cases of HCC patients with cirrhosis (58.9%) was higher, but not significantly, than that in those without cirrhosis (33.3%). The mean age of HBsAg-positive cases was 5 yr less than that of HBsAg-negative cases, the age distributions therefore being significantly differ ent. (Author abstract) (43 Refs)

32. DYNAMICS OF SERUM ALPHA-FETOPROTEIN DURING SPONTANEOUS HEPATOCELLULAR CARCINOMA DEVELOPMENT IN MICE.

Princler GL, Vlahakis G, Kortright KH, Okada S, McIntire KR
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Eur J Cancer Clin Oncol; 17(12):1241-1248 1981

C3H-AvyfB mice have been studied over their normal life span and 69% developed hepatocellular carcinoma (HCC). Forty-seven mice were bled at monthly intervals, and individual serum alpha-fetoprotein (AFP) profiles are presented for 36 animals. Most of these profiles are quite irregular. Sixty percent of the 15 male mice had a transient serum AFP elevation at 5 mo, reaching a mean of 289 ng/ml, compared to a mean of 208 ng/ml for those male mice without a transient AFP elevation and a mean of 185 ng/ml in male mice at 2-4 mo of age. All of these male mice and others were tested for murine hepatitis virus and found to be negative. Mice with this early AFP peak tended to have a lower incidence of HCC and much lower AFP values later in life than those not having an early peak, but this difference was not statistically significant. Of the mice whose serum AFP concentration exceeded 300 ng/ml beyond 6 mo of age, 23% (9/39) experienced a subsequent pronounced decline in AFP, averaging 74% of previous peak values for males and 44% for females. Of the 39 mice evaluated, 35 were autopsied and 50% (4/8) of these 'serum AFP regressors' had microscopic evidence of lymphocytic infiltration in their livers, as compared to 15% (4/27) of the 'nonregressors' that had a similar change. (Author abstract) (15 Refs)

33. REGULATION OF RAT ALPHA-FETOPROTEIN PRODUCTION BY METHIONINE DURING ETHIONINE-HEPATOCARCINOGENESIS.

Miyazaki M, Watanabe A
Div. Pathology, Cancer Inst., Okayama Univ., Okayama 700, Japan
Int J Cancer; 29(2):213-216 1982

The levels of serum alpha-fetoprotein (AFP) in rats were determined during hepatocarcinogenesis with ethionine, and the effects of methionine administration on serum AFP elevation in these animals were studied with the aim of investigating regulatory mechanisms of AFP production during carcinogenesis. Elevation of serum AFP was observed 6 wk following the start of feeding a diet containing 0.25% ethionine and again at the 22nd wk of feeding, when a well-differentiated hepatoma had already developed. These biphasic elevations of serum AFP concentrations in rats fed a 0.25% ethionine-containing diet decreased abruptly and significantly following a change to the basal diet either supplemented with or without 0.7% methionine. The possibility that regulation of AFP production in these rats may correlate with methionine metabolisms is discussed on the basis of the experimental data obtained. (Author abstract) (17 Refs)

34. HEPATOCELLULAR CARCINOMA ARISING IN NONCIRRHOTIC AND HIGHLY CIRRHOTIC LIVERS: A COMPARATIVE STUDY OF HISTOPATHOLOGY AND FREQUENCY OF HEPATITIS B MARKERS.

Okuda K, Nakashima T, Sakamoto K, Ikari T, Hidaka H, Kubo Y, Sakuma K, Motoike Y, Okuda H, Obata H
Dept. Medicine, Chiba Univ. Hosp., Chiba, Japan
Cancer; 49(3):450-455 1982

Hepatocellular carcinoma (HCC) associated with cirrhosis and HCC developing in a noncirrhotic liver may have differing pathogeneses. To study this possibility, 426 autopsied cases of HCC were investigated. Of these, 45 livers were not cirrhotic, 50 were highly cirrhotic (liver wt less than 99 g), and the remaining 331 were cirrhotic but not so highly. The av age was significantly older in the highly cirrhotic group, suggesting a longer premalignant period of chronic liver disease. The liver wt in the noncirrhotic group was about 3.5 times that in the highly cirrhotic group. Hepatitis B surface antigen was positive in serum in only 9.3% and in liver tissue in 10% in the noncirrhotic cases, the positivity rate being much lower compared with other groups (p less than 0.005-0.01), yet antibody to HB core was positive in 90%. The antibody titers were low, however, indicating that these noncirrhotic patients had in the past had HB virus (HBV) infection with no residual chronic B hepatitis. Analysis of the grades of anaplasia of cancer tissue demonstrated an inverse correlation between the degree of fibrosis and grade of anaplasia, i.e., the more advanced the fibrosis, the less anaplastic the cancer. These data suggest that HCC arising in highly cirrhotic livers and in noncirrhotic livers have different pathogenetic backgrounds, and that HBV infection, even though transient, has a certain role in hepatocarcinogenesis. The generally held conjecture that HCC in a noncirrhotic liver is caused by nonviral carcinogens and HCC arising on the ground of cirrhosis is due to HBV seems untenable in such a simple concept. (Author abstract) (27 Refs)

35. THE RELATIONSHIP OF HEPATITIS B ANTIGENS TO HEPATOCELLULAR CARCINOMA AND LIVER CIRRHOSIS - A CYTOCHEMICAL EXAMINATION OF LIVER OF 462 CASES.

Yan R, Gan L, Huang G
Dept. Cancer Res., Guangxi Medical Coll., Guangxi Province, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(2):143 1981

Using Shikata's and Gomori's staining methods, hepatitis B surface antigens (HBSAG) were analyzed in 462 liver specimens from various sources in order to study the relationship between hepatitis B, liver cirrhosis and hepatoma. Among the hepatoma patients (192 cases), 71.8% were complicated with liver cirrhosis, with an HBSAG-positive rate of up to 76.5%. It was concluded that the occurrence of hepatoma is closely related to HBSAG, especially when it is present in liver cirrhosis. (no Refs) (In CHI)

36. HUMAN BLOOD GROUPS M-, N-, T-, AND TN-SPECIFIC SUBSTANCES IN LIPIDIC EXTRACTS OF LINE 10 HEPATOCARCINOMA OF STRAIN 2 GUINEA PIGS.

Springer GF, Cantrell JL, Desai PR, Tegtmeyer H
Immunochemistry Res., Evanston Hosp., Evanston, IL, 60201
Clin Immunol Immunopathol; 22(1):9-19 1982

Live line 10 (L-10) hepatocarcinoma cells of Strain 2 guinea pigs carry immunoreactive human blood group T (Thomsen-Friedenreich)- and Tn-specificities on their surface as determined with human antisera. Disintegrated L-10 cells show in addition M and N activities; this indicates their presence within the tumor cells. Blood groups S and D(Rh0) activities were not demonstrable. M and N but not Tn an T specificities were also found in normal submaxillary and sublingual glands, kidney, and liver of Strain 2 guinea pigs. After extraction of L-10 carcinoma cells with n-butanol-water, all activities resided in the organic phase. Extraction of the organic phase by Sevag's deproteinization procedure yielded nearly eight times as much active material (by wt) in the chloroform layer as in the aqueous layer. Depending on the antisera used, M and N activities of the extracts amounted to 10 to greater than 100% of authentic red cell M and N glycoproteins, Tn activity to approx 75%, and T activity to between 5 and 10% of that of human red blood cell-derived T antigen. The active extracts had less than 0.75% protein and less than 3.50% ash. We report two novel findings: (a) the occurrence of M and N specificities in nonprimates, and (b) the association of these specificities with lipidic substances. (Author abstract) (48 Refs)

37. FUNCTIONAL ALPHA1 PROTEASE INHIBITOR PRODUCED BY A HUMAN HEPATOMA CELL LINE.

Glasgow JE, Bagdasarian A, Colman RW
Albert Einstein Medical Center, Korman Building, York and Tabor Roads, Philadelphia, PA, 19141
J Lab Clin Med; 99(1):108-117 1982

Alpha1 protease inhibitor antigen was identified in the culture medium of the human ascites hepatoma cell line SK-HEP-1. Trypsin inhibitory activity and alpha1pI antigen accumulated in serum-free medium concomitantly over a period of several days. Radioactive alpha1PI antigen was detected in conditioned medium from cultures supplemented with 35S-L-methionine, indicating synthesis and release of the protein. alpha1PI antigen in conditioned medium appeared to be antigenically identical to that in human plasma, and the newly synthesized (radiolabeled) antigen co-migrated with plasma alpha1PI after immunoelectrophoresis or SDS-polyacrylamide gel electrophoresis. Moreover, evidence is presented that the synthesized inhibitor exhibits functional activity, since the 35S-labeled alpha1PI in conditioned medium complexes with trypsin. We concluded that SK-HEP-1 cells in culture produce functionally active alpha1PI which may be identical to that in plasma. (Author abstract) (25 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

38. LAPAROSCOPIC CHANGES OF THE LIVER DURING HEPATOCARCINOGENESIS FED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE OR 2-FLUORENYLACETAMIDE (MEETING ABSTRACT).

Numa Y, Okita K, Ando K, Fukumoto Y, Kodama T, Takemoto T
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The hyperplastic liver nodule has been focused as the precancerous lesion in rats during hepatocarcinogenesis. However, there is not any direct evidence that hepatoma is exactly induced in this nodule. Therefore, we applied the laparoscopic method to observe the course during hepatocarcinogenesis. The small diameter fiberscope (diameter 4 mm) and rigid laparoscope were made by the courtesy of Machida Co (Tokyo). Moreover, a biopsy method under direct vision was devised for the consecutive histological study of the nodules. Tentatively, laparoscopy revealed 2 kinds of nodules showing red or gray with or without vessels on their surface. Moreover, the biopsied specimen was sufficient to analyze biochemical multiplicity of the nodules. (no Refs)

39. SEQUENTIAL CHANGES IN HISTOCHEMICAL LOCALIZATION OF EPOXIDE HYDROLASE AND GAMMA-GLUTAMYL TRANSPEPTIDASE DURING HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Noda K, Fukumoto Y, Oki K, Takemoto T
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The subject of this study is the clarification of roles about microsomal epoxide hydrolase (EH) in promotion stage of chemical carcinogenesis. After diethylnitrosoamine (DEN) (200 mg/kg, ip), partial hepatectomy and 2-acetylaminofluorene (2-AAF) feeding (0.02%, 2 wk) were done. From 1 to 8 wk rats were sacrificed and liver tissues were fixed with ethanol. By means of peroxidase-antiperoxidase method, the changes of EH localization were studied, and also gamma glutamyl transferase (GGT) was examined by the consecutive liver tissue sections. From 2 wk the regression of EH was recognized in each focus. And in major parts of foci, GGT localized in those EH-negative areas as if in compensation. Furthermore, the change in a remodeling stage was studied with the intermittent 2-AAF feeding (0.05%) regimen. The different localization of the two kinds of marker enzymes is discussed. (no Refs)

40. PATTERN OF GLYCOGEN AND IRON ACCUMULATION IN EARLY APPEARING BHC INDUCED LIVER LESIONS AND LIVER TUMOURS.

Nigam SK, Babu KA, Bhatt DK, Karnik AB, Thakore KN, Lakkad BC, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health, Ahmedabad 380016, India
Indian J Med Res; 74:289-296 1981

Inbred Swiss mice were fed diet containing 500 ppm of technical grade BHC (hexachlorocyclohexane) for 8 mo when typical liver tumor developed. Animals were weighed at the start of the experiment and prior to sacrifice. These animals were sacrificed at different time intervals and their liver was weighed to find out the liver weight as a percentage of body wt. The liver wt increased with increased duration of BHC feeding. Liver sections were examined for glycogen and iron accumulation. In normal liver glycogen was uniformly distributed, in the hepatocytes; after BHC feeding glycogen deficient cells around central vein and excessively glycogen laden liver cells were seen in the periphery. Glycogen in these cells remained in excess even after withdrawing BHC feeding. In 6 mo tumor developed in the liver and tumor cells were completely deficient of glycogen. Similarly iron was uniformly distributed in Kupffer cells and in hepatocytes in normal liver. In hyperplastic areas Kupffer cells contained minimum iron and the tumor cells were completely deficient of iron. Thus glycogen and iron distribution followed a definite pattern on exposure to BHC. (Author abstract) (16 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

41. A STUDY ON THE LOST NUCLEAR RNA IN AZODYE-INDUCED HEPATOMA (MEETING ABSTRACT).

Akao M, Kuroda K

Department of Toxicology and Experimental Pathology, Research Institute Chemobiodynamics, Chiba University, Chiba, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

DNA-RNA competitive hybridization study with the use of terminally 32P-labeled nuclear RNA (nRNA) indicated definitely the loss of some nRNA species in 3'-Me-dimethylaminoazobenzene (DAB) induced hepatoma. No such deletion was found in the livers of rats fed 3'-Me-DAB, alone or in combination with phenobarbital. The nRNA species that were present in liver and lost in hepatoma were then fractionated. The pertinent RNAs were found to exist among those whose sedimentation coefficients were less than 14S under sucrose density gradient centrifugation, and polyacrylamide gel electrophoresis indicated that these RNAs were fast-moving low mol wt ones. (no Refs)

42. ORNITHINE OXOACID AMINOTRANSFERASE FOUND IN AH 130 ASCITES HEPATOMA CELLS.

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Biochim Biophys Acta; 714(2):356-360 1982

We found heterogenous ornithine oxoacid aminotransferase (L-ornithine: 2-oxo-acid aminotransferase, EC 2.6.1.13) in rat ascites hepatoma AH 130 cells. Compared with enzymes from normal rat tissues, this heterogenous enzyme showed larger Km values for 2-oxoglutarate, a different elution-profile upon affinity chromatography with 2-oxoglutarate, more anionic mobility upon polyacrylamide gel electrophoresis, and a clearly different salting-out property upon ammonium sulfate fractionation. Similar heterogeneity of this aminotransferase was found in human cancer cells. (Author abstract) (25 Refs)

43. ARYLAMIDASES FROM HUMAN HEPATIC AND RENAL CANCER TISSUES IN COMPARISON WITH NORMAL TISSUE ENZYME (MEETING ABSTRACT).

Sumikawa K, Yamamoto H, Hada T, Higashino K
Third Department of Internal Medicine, Osaka University School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Arylamidases were solubilized from human hepatic and renal cancer tissues by bromelain treatment, and their properties were compared with the normal tissue enzymes. An electrophoretic study showed that the most rapidly migrating activity was that of the normal liver enzyme, and that the most slowly migrating activity was that of the normal kidney one. The hepatic and renal cancer tissue enzymes yielded activity with intermediate mobility. However, the enyzmes from four sources were indistinguishable with respect to the other physicochemical and immunological properties. These results may suggest that these four enzymes were synzymes which were coded by the identical structure gene. (no Refs)

44. TURNOVER OF PLASMA MEMBRANE PROTEINS AND GLYCOPROTEINS IN NORMAL AND REGENERATING LIVER AND MORRIS HEPATOMA 7777.

Tauber R, Reutter W
Inst. fur Molekularbiologie und Biochemie, Freien Universitat, Arnimallee 22, D-1000 Berlin 33, W. Germany
Eur J Cell Biol; 26(1):35-42 1981

Insertion and loss of individual polypeptides and glycopolypeptides were investigated in the plasma membrane of hepatic tissue at three states of differentiation: (a) in normal liver, (b) regenerating liver and (c) in the Morris hepatoma 7777. Newly synthesized polypeptides and glycopolypeptides were inserted into the plasma membrane of all three tissues at different rates. In vivo labeling was performed with either L-[35S]methionine or L-[14C]fucose. Plasma membrane proteins were degraded heterogenously with at least two dynamically different classes in all three tissues. In normal liver three polypeptide bands, mol wt of 78 K, 94K and 165 K, were lost from the plasma membrane with an apparent half-life of less than 4 hr, whereas the bulk of plasma membrane proteins was degraded with an av half-life of 40 hr. In Morris hepatoma four polypeptide bands with mol wt of 22K, 36K 63K and 87K exhibited the same rapid degradation. Two of the short-lived polypeptides in liver (78K and 94K), and hepatoma (63K and 87K) were fucosylpolypeptides. There is evidence, that these two fucosylpolypeptides were lost from the plasma membrane by shedding into the cytosol. In normal liver rates of degradation of long-lived polypeptides correlated with the polypeptide mol wt, indicating that larger proteins may turn over at higher rates. In regenerating liver and hepatoma degradation of polypeptides of either high or low mol wt was inhibited to the same extent. It is concluded, that these readjustments in the relative rates of degradation of membrane polypeptides are a characteristic feature of proliferating hepatic tissue. (49 Refs)

45. A COMPARATIVE STUDY OF PLASMA MEMBRANE MG2+ -ATPASE ACTIVITIES IN NORMAL, REGENERATING AND MALIGNANT CELLS.

Ohnishi T, Suzuki T, Suzuki Y, Ozawa K
Biological Lab., Tokyo Inst. Technology, Tokyo, Japan
Biochim Biophys Acta; 684(1):67-74 1982

Plasma membranes have been prepared from rat normal liver cells, regenerating liver cells and Yoshida ascites hepatoma 66 cells after intact cells were first bound to polylysine-coated polyacrylamide beads, and the membrane-associated Mg++ -ATPase activity was assayed directly on beads with membrane attached. With plasma membranes from normal liver cells, Km for ATP and V were found to be higher than those in regenerating liver cells and hepatoma cells. Vanadate caused a different sensitivity of the activity, without an effect in normal liver cells and with an inhibition in regenerating liver cells and hepatoma cells. The activity in normal and regenerating liver cells decreased with increasing temperature above 24-30 C, while the activity in hepatoma cells continued to increase linearly in 37 C. Unlike the enzyme in normal and regenerating liver cells, the hepatoma enzyme was shown to have a higher phase transition temperature and lower activation energies. In all three kinds of cells the activity was increased by the dephosphorylation of plasma membranes and unaffected by the phosphorylation. By means of histochemical Mg++ -ATPase staining applied on polyacrylamide gels, at least three major bands which show the enzymic activity were visible in normal and regenerating liver and a single band was detected in hepatoma cells. (Author abstract) (32 Refs)

46. INTERACTION OF AFLATOXIN B2 WITH RAT LIVER DNA AND HISTONES IN VIVO.

Groopman JD, Fowler KW, Busby WF, Wogan GN
Boston Univ. Sch. Public Health, 80E Concord St., Boston, MA, 02118
Carcinogenesis; 2(12):1371-1373 1981

The interaction of aflatoxin B2 (AFB2) in vivo with rat liver nuclear macromolecules was examined in an attempt to correlate this binding with biological potency. The incorporation of [3H]AFB2 residues into rat liver histones and DNA was determined 2, 24 and 48 hr following administration of a single ip dose of 1 mg [3H]AFB2/kg body weight. At each time point, histone H1 and the total histone fraction contained 5-30-fold more [3H]AFB2 moieties than did DNA on a weight basis. Analytical reversed-phase hplc of the acid hydrolysis products resulting from AFB2 binding to DNA revealed that 85% of the radioactivity cochromatographed with the major aflatoxin B1-DNA adduct, 2,3-dihydro-2-(N7-guanyl)-3-hydroxyaflatoxin B1. These studies revealed an apparent correlation between AFB2 derived binding to DNA in vivo in rats and its potency as a toxin and carcinogen in this species. (Author abstract) (14 Refs)

47. THE EFFECTS OF BENZO(A)PYRENE ON RAT LIVER LYSOSOMES.

Carevic M, Carevic O
Res. Centre Medicine and Psychology Traffic, Sarengradska 3, 41000 Zagreb, Yugoslavia
Toxicol Lett; 10(1):41-49 1982

Male and female rats receiving ip injections of benzo(a)pyrene (BP, 10 mg/kg) showed increased release of hepatic beta-glucuronidase, beta-galactosidase, and beta-N-acetylglucosaminidase, followed by increased activities of these enzymes in blood plasma. Lysosome-enriched liver suspension incubated for 20 min at 37 C with increasing concentrations of BP (10(-7), 10(-6), and 10(-5) M) exhibited no significant changes in specific activities of these enzymes. BP, at the same three concentrations, caused increased release of the three enzymes during 20 min incubation in a concentration-dependent manner. Equal volume doses of dimethyl sulfoxide had no effect, or decreased release slightly. The observed lysosomal changes precede by several hours the onset of the altered cells or cell populations that appear in the liver approx 24 hr after BP administration. Injection of BP into rats may injure the lysolemma; injuries to the lysolemma may be an important feature of the early biochemical events in BP-initiated hepatocarcinogenesis. (29 Refs)

48. CELL CYCLE PATTERNS OF THYMIDYLATE SYNTHETASE AND 5,10-METHYLENETETRAHYDROFOLATE POLYGLUTAMATES IN CULTURED MOUSE HEPATOMA CELLS.

Priest DG, Doig MT, Ledford BE

Dept. Biochemistry, Medical University South Carolina, Charleston, SC, 29425

Experientia; 38(1):88-89 1982

The regulation of thymidylate synthetase activity was investigated throughout the first cell cycle after release from an isoleucine block in synchronous cultures of mouse hepatoma (Hepa) cells. Activity in cell extracts increased with the onset of S phase and the increased activity was attributed to a parallel increase in enzyme concentration as determined by titration with tritiated fluorodeoxyuridylate. The polyglutamate chain length of reduced folate cofactors, which could also influence thymidylate synthetase activity, was unchanged. (Author abstract) (24 Refs)

49. EUCHROMATIN PROTEIN PHOSPHORYLATION AND NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

DeLuca C, Smith GJ

Department of Pathology, University of New South Wales, New South Wales, Australia

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Non histone chromosomal proteins (NHCP) are thought to have a specific gene regulatory function. Indentification and characterization of phosphorylated NHCP may provide useful cellular markers for the early onset of neoplasia and may elucidate mechanisms of neoplasia. The experiment design involves an analysis of euchromatin protein alteration during the initial and promotional stages of chemical carcinogenesis as outlined in the Solt-Farber regime. Diethylnitrosamine (DEN) is used as the initiating agent and promoting is achieved through the dietary administration of 2-acetylaminofluorene accompanied by a non-specific growth stimulus-partial hepatectomy. The DNAse I prepared soluble transcriptionally active (euchromatin) fraction is extracted from purified nuclei, labelled with [32P] orthophosphate in primary cell suspension culture. The chromatin proteins are analyzed by two dimensional polyacrylamide gel electrophoresis and autoradiography. Preliminary observations indicate that following a single dose of DEN (200 mg/kg ip), there is acute histological damage to nuclei at one wk and complete recovery within three wk. Electron micrographs of purified nuclei confirmed these findings. Furthermore, electrophoretic analysis of control and DEN treated animals using Coomassie blue visualization of proteins, resulted in the detection of several proteins, not evident in the control animals. (no Refs)

50. ISOLATION OF NUCLEOSIDE PHOSPHOTRANSFERASES FROM CHROMATIN OF MORRIS HEPATOMA 9121 NUCLEI.

Lenger K

Instit fur Biochemische Endokrinologie, Medizinischen Hochschule Lubeck, Ratzeburger Allee 160, D-2400 Lubeck, W. Germany

Int J Biochem; 14(1):53-61 1982

Chromatin of Morris Hepatoma 9121 nuclei was obtained from isolated nuclei derived from tumors grown in male ACI rats. Thymidine phosphorylation activity of chromatin was identified in six peaks on diethylaminoethanol-cellulose chromatography. One nuclear enzyme (C) was separated into two subunits of approx 100,000 and 130,000 mol wt as estimated by calibration proteins. Density gradient centrifugation and Sephadex-G 150 gel filtration gave similar results, and confirmed the split nature of enzyme C. Peak activity of the enzyme was at pH 6.8-7.0, the best phosphate donors were AMP and ADP, and the preferred substrate was deoxyguanosine. Enzyme C is apparently a deoxyguanosine phosphotransferase and its reaction mechanism was suggested by the velocity of 14C-thymidine phosphorylation to be allosteric with positive cooperativity. (28 Refs)

51. CHRONIC OR ACUTE ADMINISTRATION OF VARIOUS DIALKYLNITROSAMINES ENHANCES THE REMOVAL OF O6-METHYLGUANINE FROM RAT LIVER DNA IN VIVO.

Margison GP

Paterson Lab., Christie Hosp., Holt Radium Inst., Manchester M20 9BX, England

Chem Biol Interact; 38(2):189-201 1982

The effect of pretreatment of rats with various symmetrical dialkylnitrosamines on the repair of O6-methylguanine produced in liver DNA by a low dose of [14C]dimethylnitrosamine (DMN) has been examined. DMN, diethylnitrosamine (DEN), dipropylnitrosamine (DPN) or dibutylnitrosamine (DBN) were administered to rats for 14 consecutive weekdays at a daily dose of 5% of the LD50. Animals were given [14C]DMN 24 hr after the last dose and were killed 6 hr later. DNA was extracted from the liver and analyzed for methylpurine content after mild acid hydrolysis and Sephadex G-10 chromatography. While the amounts of 3-methyladenine and 7-methylguanine were only slightly different from controls, the amounts of O6-methylguanine in the DNA of the dialkylnitrosamine pretreated rats were about 30% of those in control rats, indicating a considerable increase in the capacity to repair this base. Liver ribosomal RNA from control and dialkylnitrosamine pretreated rats contained closely similar amounts of O6-methylguanine suggesting that the induced enzyme system does not act on this base in ribosomal RNA in vivo. Pretreatment with these dialkylnitrosamines also enhanced the repair of O6-methylguanine in liver DNA when they were given as a single dose (50% of the LD50) either 3 or 7 days before the [14C]DMN. In addition, single low doses of DMN or DEN (5% of the LD50) given either 1 or 6 days before [14C]DMN increased O6-methylguanine repair and the magnitude of the effect after DEN was similar to that produced by the other pretreatment schedules. The possible mechanism(s) of the induction of O6-methylguanine repair and its relation to hepatotoxicity, DNA alkylation, carcinogenesis and the adaptive response in Escherichia coli are discussed. (Author abstract) (42 Refs)

REVIEWS AND OTHER RELATED STUDIES

52. LIVER AND ALCOHOL.

Manenti F, Villa E
Cattedra di Gastroenterologia, Universita di Modena, Modena, Italy
Fegato; 27(2):95-118 1981

Effects of alcohol on the liver were reviewed under the following headings: metabolism of ethyl alcohol (EA) and its consequences in liver cells (effect of EA on lipid, protein, and glycoprotein metabolism; EA and liver fibrosis; and effect of EA on drug metabolism), pathogenesis of liver damage due to EA (genetic factors and immunologic characteristics), macroscopic and microscopic morphology of alcoholic hepatopathy, clinical picture [liver steatosis, acute alcoholic hepatitis, cirrhosis, and associated pathologies (primary liver carcinoma)], and therapeutic possibilities in alcoholic hepatopathy. (79 Refs) (In ITA)

53. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

Toxic and carcinogenic effects of ethylene dibromide (EDB) are reviewed. Recent experimental data has reinforced the conclusion that EDB is carcinogenic in animals and that EDB should be treated as a potential occupational carcinogen in the workplace. A ceiling limit of 0.13 ppm (1.0 mg/cubic meter) over any 15 min sampling period and use of appropriate controls to reduce worker exposure are recommended. Studies have shown a high mortality rate and a statistically significant increase in incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity in rats exposed to EDB by inhalation at 20 ppm and fed the standard rat diet. Addition of disulfiram (0.05% by wt) to the diet resulted in an approx ten-fold increase in incidence of hepatocellular carcinomas over exposure to EDB alone. The increased interaction may not necessarily be restricted to disulfiram but may occur with similarly structured compounds such as Thiram, a fungicide and seed disinfectant. Epidemiologic studies of EDB in humans have been inconclusive because of small cohort size, incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects. Gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hr for all cell stages tested. (16 Refs)

54. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.

Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

Evidence that the initiation of the carcinogenic process by nitrosamines is linked to the metabolic competence of the target tissue or cell to convert carcinogens into mutagenic metabolites, and to the binding of those metabolites to cellular DNA is reviewed. Alkylation of DNA occurs at the N-1, N-3, and N-7 positions of adenine; N-3, N-7, and O6 of guanine; N-3 and O2 of cytosine; N-3, O4, and O2 of thymine; and the phosphate groups. The initial proportion of each DNA adduct depends upon the alkylating agent. Alkylation at the oxygen atoms of DNA bases is more critical than alkylation at other positions in the mutagenesis and carcinogenesis induced by N-nitroso compounds. Tissues in which tumors occur more frequently are those in which O6-alkylguanine persists longest in DNA. The more rapid removal of O6-methylguanine from DNA of rat liver is associated with the absence of tumor production in this organ by a single dose of dimethylnitrosamine (DMN). Significant incidence of liver tumors is observed if the same dose is given 24 hr after partial hepatectomy. Data indicate that the rate of disappearance of 7-met hylguanine from the liver or extrahepatic tissues is independent of DMN dose; O6-methylguanine is lost from DNA more rapidly after a low dose of DMN. The removal of O6-methylguanine from DNA can be affected by pretreating the animals with N-nitroso compounds. The modulation of DNA repair processes is discussed in relation to the tissue-specific carcinogenic effect of N-nitroso compounds. (132 Refs)

55. SOME RECENT PROGRESS ON THE STUDIES OF HEPATITIS.

Huang Z
Inst. of Virology, Chinese Acad. of Medical Sciences, Beijing, People's Republic of China
Zhonghua Weishengwuxue He Mianyixue Zazh; 1(2):140-145 1981

Recent progress on hepatitis research is reviewed. Work done in the United States is highlighted. Topics discussed include: (1) Hepatitis A, cultivation of hepatitis A virus and epidemiologic studies on its immunology, (2) Non-A and Non-B hepatitis, its modes of transmission and clinical characteristics, and (3) Hepatitis B, structure and function of hepatitis B virus, viral gene expression in infected liver cells, vaccines preparation, and relation of hepatitis B to liver cancer. (15 Refs) (In CHI)

56. ALPHA FETOPROTEIN. A SUMMARY OF CURRENT KNOWLEDGE AND CLINICAL VALUE.

Labadie P
Unite fonctionnelle d'hormonologie, Hopital Pellegrin-Tripode, 33000 Bordeaux, France
Rev Prat; 31(55):4057-4065 1981

The use of alpha fetoprotein (AFP) in the diagnosis and course of certain tumors and infections is reviewed. AFP levels rise to 30-3,000 nanog/ml in the plasma, saliva, and urine of patients with malignant primary hepatomas although there is no correlation between tumor size and AFP levels. Higher AFP levels have also been measured in patients with teratoblastomas, and some tumors of the digestive tract. A rise in AFP levels has not been found to correlate clearly with tumor recurrence or metastases. (4 Refs) (In FRE)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).
NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.
Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.
Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.
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NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.
Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
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12. THE SMOKING-INDUCED EPIDEMIC.
Doll R
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Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
Kaw JL
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14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):133-139 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.
Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.
Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
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18. POLYOMA T ANTIGENS.
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Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
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19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.
James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Addenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.
Office of Technology Assessment
Office of Technology Assessment, Washington, DC
Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400:, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.
Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.
Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
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OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.
Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART 1.
Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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ORGAN SITE CARCINOGENESIS

Liver

SERIES CK16 No. 82/07

JULY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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16/82/07

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. A COMPARISON OF THE PATHOBIOLOGY AND EPIDEMIOLOGY OF CANCERS ASSOCIATED WITH VIRUSES IN HUMANS AND ANIMALS.

Essex M, Gutensohn N
Dept. Microbiology, Harvard Univ. Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Prog Med Virol; 27:114-126 1981

Several oncogenic viruses in animals (chicken, cat, ox, gibbon, rabbit) are discussed in terms of characteristics and epidemiological features and are compared with human malignancies most likely to be caused by a virus (leukemias, Hodgkin's disease, Burkitt's lymphoma, cervical cancer, nasopharyngeal cancer, and primary hepatocellular carcinoma). Cancers of industrialized countries tend to be associated with environmental or dietary agents, whereas those in the developing world are likely to be of viral origin, suggesting that a vaccination program would have a profound effect in developing countries. (52 Refs)

2. HEPATITIS B INFECTION AND PRIMARY LIVER CANCER.

Maupas P, Melnick JL
Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:1-5 1981

The statistical relationship between hepatitis B infection and primary liver cancer (PHC) is clear. Evidence from a recent workshop in Dakar, Senegal, is presented, including geographic distribution, endemiology, cirrhosis, DNA and antigen, and animal viral evidence. Hepatitis B vaccines and antibody induction treatment may contribute to a reduction in PHC, even though the precise etiologic relationship between the two diseases remains unknown. (no Refs)

3. EPIDEMIOLOGY OF PRIMARY HEPATOCELLULAR CARCINOMA IN SENEGAL.

Diop H, Denis F, Barin F, Perrin J, Chiron JP, Goudeau A, Coursaget P, Maupas P
Service de Medecine Interne, Faculte de Medecine et Pharmacie, Dakar-Fann, Senegal
Prog Med Virol; 27:35-40 1981

Primary hepatocellular carcinoma (PHC) appears to be a very common tumor in Senegal. PHC is more often found in the age group 31-40 yr, with a mean age of 38 yr. Male cases of PHC predominate in liver-cell cancer in Dakar. PHC occurs predominantly in the Wolof ethnic group, which also account for most of th patients hospitalized in Dakar and the most prominent ethnic group in the Cap-Vert area. PHC exists in in Senegal in every socioeconomic group but is more prevalent among the poorer social classes. Increased numbers of PHC hospitalizations in Dakar occur in November, December, January, and February. In 90% of PHC cases there is an underlying hepatic cirrhosis or fibrosis. (18 Refs)

4. ALCOHOL AND CANCER.

MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

Epidemiologic and experimental studies are reviewed. Heavy alcohol consumption is assessed as a prime carcinogen of the esophagus and the mouth, a contributor of some type to carcinogenesis of the pharynx and larynx, and a cause of primary hepatocellular carcinoma in conjunction with hepatic cirrhosis. Associations with cancer of other portions of the gastrointestinal tract, the breast, thyroid, kidney, and bladder are equivocal. The actual mode of action is not known; possibilities are discussed. (30 Refs)

5. THE CAUSES OF PRIMARY HEPATOCELLULAR CARCINOMA IN GREECE.

Trichopoulos D

Dept. Hygiene and Epidemiology, Univ. Athens Medical Sch., Goudi, Athens 609, Greece

Prog Med Virol; 27:14-25 1981

Epidemiologic studies undertaken in Greece and concerning the etiology of PHC are reviewed, and the broader implications of their findings are discussed. HBV is the most important etiologic factor worldwide with an associated relative risk of about 15. Aflatoxin may be an important etiologic factor in Africa and Asia, mainly for PHC cases without indication of active HBV infection. In Europe and the USA a minority of PHC cases without indication of active HBV infection may be due to alcohol drinking, but there is now evidence that cigarette smoking is also related to this type of cancer with an associated relative risk of about 3. (Author abstract) (48 Refs)

6. CIRRHOSIS AND PRIMARY LIVER CELL CARCINOMA IN TAYSIDE. A FIVE YEAR STUDY.

Hislop WS, Masterton N, Bouchier IA, Hopwood D

Dept. Medicine, Ninewells Hosp. and Medical Sch., Dundee, Scotland

Scott Med J; 27(1):29-36 1982

Despite Scotland's well-recognized alcohol problem, there is scant information on the etiology of cirrhosis in this country. This study of 222 patients, reviewed 197 cases presenting as cirrhosis and 25 cases presenting as primary liver cell carcinoma (PLCC) in the East Tayside are of Scotland between 1975 and 1979. The survey was based on an analysis of all histologically proven cases of cirrhosis and PLCC encountered during a 5-yr period. There was a constant rate of presentation of cirrhosis of about 40 new patients per yr, with a stable pattern of etiology. About 55% were due to alcohol, and there was no significant change in this proportion over the study. No evidence was found for an increasing female susceptibility or earlier female morbidity in alcoholic cirrhosis. Cryptogenic cirrhosis, cardiac cirrhosis and secondary biliary cirrhosis were more often diagnosed at post mortem. Ninety one percent of patients with primary biliary cirrhosis were females, but the expected male preponderance in hemochromatosis was not present. In addition to the 25 patients presenting with PLCC, three of the cirrhotic patients developed the tumor by the end of 1979. Seventy one percent of PLCC case arose in already cirrhotic livers, none were HbsAg positive. Bronchopneumonia, hepatic failure, gastrointestinal bleeding and cardiac failure were the most frequent causes of death. (Author abstract) (39 Refs)

7. FREQUENCY AND TREATMENT OF PRIMARY HEPATOCELLULAR CARCINOMA IN LOS ANGELES.

Tong MJ, Chlebowski RT, Weissman JY, Bateman JR
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:6-13 1981

The majority (85%) of cases of primary hepatocellular carcinoma (PHC) in Los Angeles involved prior cirrhosis; alcoholism was a related factor in most cases of PHC reported from 19 18 to 1973. Experience with 5-fluorouracil and adriamycin semustine chemotherapy indicated that successful treatment of PHC has not been found. Survival was longer in patients with serum bilirubin levels of less than 2 mg% than those with greater than 2 mg% and in patients who were negative for hepatitis B surface antigen than those who were positive. (25 Refs)

8. ARSENIC-RELATED HEPATIC ANGIOSARCOMA.

Falk H, Caldwell GG, Ishak KG, Thomas LB, Popper H
Chronic Diseases Div., Centers Disease Control, 1600 Clifton Road, NE, Atlanta, GA, 30333
Am J Industr Med; 2(1):43-50 1981

This epidemiological study (highlights only) was conducted to provide additional evidence for arsenic being one cause of hepatic angiosarcoma (HAS). Pathological samples from 350 cases originally diagnosed as HAS in the United States, mostly during 1964-1974, were reexamined. Epidemiological followups (published separately) were made on the 168 confirmed cases involving deaths during 1964-1974. Six cases were attributed to arsenic exposure, five adults from therapy for asthma or psoriasis involving imbibing Fowler's medicine (potassium arsenite), and one child with environmental exposure. Of the five therapy cases (four males and one female, 41-58 yr old), length of therapy and latency period were known only for the males, 10-17 yr and 12-24 yr, respectively. Idiopathic HAS tended to appear much later in life, in the 70s. Four male farmers known to have used Paris green or other unspecified arsenicals for long periods were 68-79 yr old at death from HAS. Two other confirmed cases with deaths prior to 1964 also involved males aged 42 and 50 yr with histories of 6 and less than 15 yr, respectively. The results were taken as supportive of a 1957 report involving autopsies on German vineyards, some dying from HAS and all having both used arsenical insecticides and regularly imbibed a beverage made from the grape skins. (27 Refs)

9. LIVER-FLUKE INFECTION AS AN AETIOLOGICAL FACTOR IN BILE-DUCT CARCINOMA OF MAN.

Flavell DJ
Winches Farm Field Station, London Sch. Hygiene and Tropical Medicine, 395 Hatfield Rd., St. Albans, Herts AL4 0XQ, England
Trans R Soc Trop Med Hyg; 75(6):814-824 1981

Evidence for an etiologic relationship between liver fluke infections (Clonorchis sinensis in southern China, Korea, and Japan; Opisthorchis viverrini in northeast Thailand) and primary cholangiocarcinoma of the liver is discussed. The etiology of cholangiocarcinomas arising in association with these trematodes is multifactorial. In the case of Opisthorchis, when freshwater ciprinoid fish containing metacercariae are eaten undercooked or raw, the metacercariae excyst in the duodenum and the juvenile flukes migrate through the common bile duct and extrahepatic biliary system to the intrahepatic bile ducts, where they mature and lay their eggs. For both parasites, the malignant transformation of infected bile ducts may initially involve a high turnover of hyperplastic biliary epithelial cells, caused directly by the parasite. This process may be further stimulated by a low protein intake by the host. The hyperplastic and proliferating bile ducts may be susceptible to the action of carcinogen(s) present at levels too low to induce cholangiocarcinomas in uninfected persons. Such carcinogens may be naturally occurring or they may form in vivo from ingested precursor molecules or endogenous substances. The host's immunologic status may also be affected by the infection, which may play a role in tumorigenesis. (77 Refs)

10. HEPATIC ADENOMA ASSOCIATED WITH ORAL CONTRACEPTIVES.

Woodyer AB
St. James's Hosp., London, England
J R Coll Surg Edinb; 27(1):59-60 1982

Hepatic adenoma associated with oral contraceptives was diagnosed in a 26-yr-old West Indian girl who presented with a 5-yr history of increasingly severe and frequent right hypochondrial pain. The serum alphafetoprotein concentration was 25 ug/liter and an ultrasound liver scan showed a solid mass arising from the lateral portion of the left lobe, well circumscribed, displacing the porta hepatis and gallbladder laterally and with an echo pattern similar to that of normal liver. The tumor was excised with a wedge of normal liver tissue. At follow-up 18 mo after operation no further abdominal pain and no sign of tumor recurrence was reported. (4 Refs)

11. REGRESSION OF LIVER CELL ADENOMA. A FOLLOW-UP STUDY OF THREE CONSECUTIVE PATIENTS AFTER DISCONTINUATION OF ORAL CONTRACEPTIVE USE.

Buhler H, Pirovino M, Akovbiantz A, Altorfer J, Weitzel M, Maranta E, Schmid M
Dept. fur Innere Medizin, Medizinische Poliklinic, Universitatsspital, Ramistrasse 100, 8091 Zurich, Switzerland
Gastroenterology; 82(4):775-782 1982

Three consecutive young female patients with unresected liver cell adenoma and a history of contraceptive use of several years' duration were followed up over a period of 2-4.5 yr after withdrawal of hormonal medication. One patient presented multiple adenomas and in another, the adenoma was associated with a Budd-Chiari syndrome due to bilateral thrombotic hepatic vein occlusion. Complete regression of the adenomas was documented in all three patients by ultrasonography, liver radionuclide scan, laparoscopy, or computerized tomography. It is concluded that, in selected cases, conservative management after withdrawal of hormonal contraception may be a valid alternative to surgical therapy. (Author abstract) (23 Refs)

12. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.

Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

Epidemiologic studies of structural analogs of vinyl chloride (VC) are reviewed. Analogs included epichlorohydrin (ECH), trichloroethylene (TCE), vinylidene chloride (VDC), ethylene dibromide (EDB), perchloroethylene (PCE), and carbon tetrachloride (CCl4). Occupational and industrial uses of the compounds include manufacture of epoxy resins (ECH), copolymers and fibers (VDC), petroleum products (EDB), and pesticides (EDB). Other uses include metal degreasing (CCl4, TCE, and PCE) and dry cleaning (PCE and formerly, TCE and CCl4). Bioassays in experimental animals have demonstrated induction of tumors at multiple sites by EDB and CCl4, in the respiratory tract by EDB and ECH, and in the liver by VDC, EDB, TCE, PCE, and CCl4. Studies of workers exposed to ECH or dry cleaning solvents suggest an increased risk of lung cancer, but the increase is not significant, possibly due to sample size. Studies of workers exposed to the other compounds have not given positive evidence of carcinogenicity. All studies have been characterized by insensitivity to increases in mortality because of small sample size. In some studies workers were exposed to more than one suspected carcinogen, making interpretation of results difficult. Estimation of qualitative risk to humans due to specific compounds should be based on experimental animal studies rather than on human epidemiological studies. (17 Refs)

13. EPIDEMIOLOGY OF HEPATIC ANGIOSARCOMA IN THE UNITED STATES: 1964-1974.

Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, Caldwell GG
Chronic Diseases Div., Center Environmental Health, Centers Disease, Control, Public Health Service U. S. Dept. Health and Human Services, Atlanta, GA, 30333
Environ Health Perspect; 41:107-113 1981

The occurrence of hepatic angiosarcoma (HAS) in the United States was studied for the period 1964-1974. Death certificates were reviewed in 22,432 cases of death due to liver tumors. Based on examination of medical records and pathological specimens, 168 cases of HAS were confirmed. Of cases identified as HAS on death certificates, only 42% were confirmed as HAS by other evidence; 50% were confirmed as not HAS. Only 23% of confirmed cases of HAS would have been identified by a search of death certificates alone. Inadequacies in epidemiological studies are indicated. HAS occurred predominantly in men (male:female ratio 3:1) and more frequently in the younger age groups. The mean age was 50.1 yr for women and 57.9 yr for men. Of 127 men with HAS, 12 had been exposed to vinyl chloride (VC), 15 to Thorotrast (TT), 4 to inorganic arsenic (As), and 3 to androgenic-anabolic steroids (AAS); 93 cases were classified as idiopathic. Of 41 women with HAS, 5 had been exposed to TT, 2 to As, and 1 to AAS; 33 cases were classified as idiopathic. A relationship between HAS and VC, TT, or AAS was more common in the latter part of the study period, probably due to recent introduction of VC and AAS and a long latency period for TT. The mortality rate for HAS was 0.75 cases/10(7) population/yr. The mortality rate was apparently higher in industrialized areas of the Northeast and Midwest and lower in farming states and the South; differences in rates for different areas may have been due to reporting methods rather than to actual differences in occurrence. Four agents have been identified as probable causative factors in HAS, but 75% of cases are of uncertain etiology. (28 Refs)

14. THE BRITISH HEPATIC ANGIOSARCOMA REGISTER.

Baxter PJ
Chronic Diseases Div., Special Studies Branch, Center Disease Control, Atlanta, GA, 30333
Environ Health Perspect; 41:115-116 1981

A register has been established to record cases of hepatic angiosarcoma (HAS) in Britain. Thirty-five cases of HAS in patients dying during the period 1963-1977 have been confirmed. HAS was related to exposure to vinyl chloride monomer (VCM) in two cases and to in administration of Thorotrast (a colloidal suspension of thorium dioxide) in eight cases. Two additional cases associated with exposure to VCM were confirmed in 1978-1979. (7 Refs)

15. ANGIOSARCOMA OF THE LIVER: A SIGNAL LESION OF VINYL CHLORIDE EXPOSURE.

Vianna NJ, Brady J, Harper P
Bureau Environmental Epidemiology, New York State Dept. Health, Tower Building, Empire State Health Plaza, Albany, NY, 12237
Environ Health Perspect; 41:207-210 1981

The association between exposure to vinyl chloride (VCM) and subsequent occurrence of angiosarcoma of the liver (ASL) is reviewed. Although ASL is a rare tumor, some evidence suggests that incidence of ASL is increasing. ASL occurs more frequently among workers occupationally exposed to VCM than among the general population. ASL may also be related to low-level, nonoccupational exposure to VCM. Other disorders possibly associated with exposure to VCM include cancers of the digestive, respiratory, neurologic, and lymphatic systems. (39 Refs)

16. GERMAN INVESTIGATIONS ON MORBIDITY AND MORTALITY OF WORKERS EXPOSED TO VINYL CHLORIDE.

Weber H, Reinl W, Greiser E
Staatlicher Gewerbearzt, Dusseldorf, W. Germany
Environ Health Perspect; 41:95-99 1981

Morbidity and mortality among workers of German or Austrian nationality exposed to vinyl chloride monomer (VCM) were studied. Standardized mortality ratios (SMR) were calculated. SMR for workers exposed to VCM were compared with those for the West German male population, chemical workers not exposed to VCM, and workers exposed to polyvinyl chloride (PVC). Cause of death could not be determined in 7.3-13.1% of cases. Data from VCM and PCV workers did not show a 'healthy worker' effect. Among VCM workers, S MR were elevated for malignancies of the lymphatic and hematopoietic systems and for malignancies of the gastrointestinal (GI) tract. The increase in SMR for GI cancers was due to an increase in deaths due to liver cancers. SMR for liver cancers was also somewhat elevated for workers not exposed to VCM; cause of the elevation was uncertain. SMR for ischemic heart disease was elevated for all three groups of workers. SMR for liver cancers increased with time of exposure to VCM, suggesting a time-response relationship. A dose-response relationship could not be established due to lack of dose determinations. SMR for cancers in general and for liver cancers were particularly high for men 35-44 yr old. A study of morbidity indicated 269 cases of suspected occupational disease among 6,500 workers in VCM or PVC production and 42,800 workers in PVC processing. (2 Refs)

17. MUTAGENICITY AND TERATOGENICITY OF VINYL CHLORIDE MONOMER (VCM): EPIDEMIOLOGICAL EVIDENCE.

Clemmesen J
(c/o P. H. Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 98(1):97-100 1982

While there is little evidence to attribute isolated cases of hepatic angiosarcoma to to vinyl chloride monomer (VCM) exposure, it would be important if mutagenic or teratogenic effects of VCM could be demonstrated in the surroundings of factories or in the domestic environment of workers. In support of this thesis, a review of epidemiological studies was made to find supportive evidence in the form of excess infant deaths or birth defects. Although excess birth defects were found in an Ohio study, these could not be attributed to polyvinyl chloride (PVC) plants due to the nonuniform distribution within communities having plants and those without them up to 12 miles away. Although excess CNS-malformation in newborns was found in another study, in one of the towns with two PVC plants, none of the parents of involved patients worked at the plants. An attempt to determine infant death rates from pregnancies initiated before and after exposure of the same fathers to VCM or PVC fabrication have been confused by a number of factors. It was concluded that none of these studies were supportive of VCM or PVC plants being responsible for isolated hepatic angiosarcoma, excess infant death rates, or excess birth defects. (8 Refs)

18. OBSERVATIONS OF THE SITE-SPECIFIC CARCINOGENICITY OF VINYL CHLORIDE TO HUMANS.

Infante PF
Office Carcinogen Identification and Classification, Health Standards, Program, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:89-94 1981

Studies of site-specific carcinogenicity of vinyl chloride (VC) are reviewed. Problems encountered included relative insensitivity to carcinogenic response at low risk sites due to small sample size, and characteristics of method and design that prevent adequate interpretation of results. Restriction of disease definition resulted in obscuring some sites that might otherwise have shown significant excess risk. Four of eight studies indicated a significant risk of liver cancer following exposure to VC, although the liver had been confirmed as a site of VC-carcinogenesis by other studies. Problems with studies of liver cancer included insufficient exposure and observation times. Some studies classify liver cancer with other cancers of the digestive tract. Overall data from at least one study of cancers of the digestive tract indicate a reduction in mortality among exposed workers. An excess of mortality due to CNS cancers was indicated by five of eight studies. Some studies classified CNS cancers with nonspecific 'other' categories. Data for lung cancer mortality suggest a significant increase in risk for workers exposed to VC. Data for cancers of the lymphatic and hematopoietic systems are suggestive but not conclusive. Overall data indicates that the carcinogenic effect of VC is not limited to the liver. (12 Refs)

TUMOR INDUCTION IN ANIMALS

19. CARCINOGENIC AND MUTAGENIC ACTIVITY OF AN ALKALOIDAL EXTRACT OF SENECIO NEMORENSIS SSP FUCHSII.

Habs H, Habs M, Marquardt H, Roder E, Schmahl D, Wiedenfeld H
Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Arzneim Forsch; 32(2):144-148 1982

The alkaloidal residue obtained after extraction of dried and pulverized Senecio nemorensis ssp fuchsii contains two pyrrolizidine alkaloids, ie fuchsisenecionine and senecionine. In a chronic experiment doses of 8 mg/kg and 40 mg/kg bw of the alkaloidal extract were given 5x a wk by gavage to male and female Sprague-Dawley rats. The study was terminated after 114 wk. Repeated serum analysis demonstrated a dose-related elevation of serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (AP). Beside its hepatatoxic effect, the treatment proved to be hepatocarcinogenic, showing female rats to be more sensitive than males. Tumors diagnosed were of hepatocellular and angiogenic origin. In age-adjusted analysis the occurrence of these neoplasms revealed a clear dose-related trend (p less than 0.00005). In the in-vitro mutagenicity test system with V79 Chinese hamster cells, the alkaloidal extract exerted a weak but dose-related mutagenic activity. Under the conditions used the alkaloidal extract of Senecio nemorensis ssp fuchsii is a genotoxic carcinogen. (Author abstract) (28 Refs)

20. LACK OF CARCINOGENICITY OF DDT IN HAMSTERS.

Cabral JR, Hall RK, Rossi L, Bronczyk SA, Shubik P
International Agency Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2 , France
Tumori; 68(1):5-10 1982

Syrian golden hamsters were fed for their lifespan a diet containing 0, 125, 250 and 500 parts per million (ppm) of DDT. The incidence of tumor bearing animals was 13% among control females and ranged between 11-20% in treated females. In control males 8% had tumors. The incidence of tumor bearing animals among treated males ranged between 17-28%. The incidence of adrenal cortex tumors showed a dose-related increase among the DDT-treated males. A liver-cell tumor and two liver hemangioendotheliomas were observed in three males treated with 250 ppm DDT. No liver-cell tumors were observed in the controls. No significant difference in tumor incidence was observed in treated vs control Syrian golden hamsters. (Author abstract) (28 Refs)

21. EFFECTS OF LONG-TERM INTAKE OF DDT ON RATS.

Cabral JR, Hall RK, Rossi L, Bronczyk SA, Shubik P
International Agency Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France
Tumori; 68(1):11-17 1982

DDT is a pesticide used in malaria-control programs throughout the world. Its potential carcinogenicity was studied in MRC Porton rats (Wistar-derived) which received dietary concentrations of 0, 125, 250 and 500 parts per million DDT (technical-grade) for life. The treatment had no adverse effects on body growth or survival rate. Various types of tumors were observed in animals in all groups: exposure to DDT resulted in statistically significant increased incidence of liver-cell tumors only in female treated rats; one such tumor was observed in control rats. No metastases of these tumors were found. (Author abstract) (30 Refs)

22. COMPARATIVE STUDIES OF NEOPLASTIC RESPONSE TO A SINGLE DOSE OF NITROSO COMPOUNDS. 7. THE EFFECT OF N-NITROSOBIS (2-HYDROXYPROPYL)AMINE IN SYRIAN GOLDEN HAMSTERS.

Pour PM, Salmasi SZ
Preclinical Res., Toxicology Dept., Sandoz AG, CH-4133 Pratteln 4, Switzerland
J Cancer Res Clin Oncol; 102(3):265-269 1982

Single sc applications of N-nitrosobis(2-hydroxypropyl)amine (BHP) caused carcinogenic effects in adult Syrian golden hamsters at doses as low as 1/40 of the LD50. The tumor spectrum decreased at lower doses, which affected the pancreas more strongly than the liver, whereas higher doses exhibited a more pronounced hepatocarcinogenicity and also induced tumors in the respiratory tract, gallbladder, kidney, and vagina. These results demonstrated a potent pancreatic carcinogenic effect of BHP at the lowest dose level. Hence, the presence of BHP in the environment, even in small quantities, should be regarded as a potential hazard to human health. (Author abstract) (9 Refs)

23. CARCINOGENICITIES OF 3-METHOXY-4-AMINOAZOBENZENE, N-HYDROXY-3-METHOXY-4-AMINOAZOBENZENE AND RELATED AZO DYES IN THE MOUSE.

Watanabe HK, Hashimoto Y, Abe I, Sato H
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 73(1):136-140 1982

The carcinogenicities of 2-methoxy-4-aminoazobenzene and 3-methoxy-4-aminoazobenzene (2-MeO-AAB and 3-MeO-AAB) and their N-hydroxy derivatives (N-OH-2-MeO-AAB and N-OH-3-MeO-AAB) were tested in (C3H x C57BL/6) F1 mice. Topical sc injections, twice weekly for 8 wk, of 4 or 8 umol of N-OH-3-MeO-AAB dissolved in 0.1 ml of olive oil containing 10% dimethyl sulfoxide induced fibrosarcomas at the site of application. Similar treatment with 3-MeO-AAB or 2-MeO-AAB as well as N-OH-2-MeO-AAB failed to induce sarcomas. Oral administration of 0.09% 3-MeO-AAB in the diet for 13 mo induced hepatic tumors in female mice but not in males. 2-MeO-AAB did not induce tumors in male or female mice. The relationship between carcinogenicity, mutagenicity, the ability to induce unscheduled DNA synthesis, and the metabolism of these azo dyes is discussed. (Author abstract) (18 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

24. EFFECTS OF AGING ON THE INDUCTION OF ANGIOSARCOMA.

Groth DH, Coate WB, Ulland BM, Hornung RW
Div. Biomedical and Behavioral Science, Natl. Inst. Occupational Safety and Health
Environ Health Perspect; 41:53-57 1981

The effects of aging on chemical induction of angiosarcoma were studied in adult Sprague-Dawley albino rats. In each of four age groups (6, 18, 32, and 52 wk old at the start of exposure), 110-128 male rats and an equal number of female rats were exposed to vinyl chloride (VC: 948 ppm, 7 hr/day, 5 days/wk for a mean duration of 24.5 wk). Equal numbers of controls were kept under identical conditions but were not exposed to VC. Rats exposed to VC did not show any significant differences in mean hematological or clinical chemistry measurements at interim sacrifice times when compared with controls. Angiosarcomas were found in 28/370 exposed males and 50/387 exposed females; among controls only one sc angiosarcoma was found. Angiosarcomas occurred more frequently with increasing age at the start of exposure. Among male rats killed at unscheduled times, the occurrence rates were 0% for 6-wk-, 0% for 17-wk-, 6.7% for 32-wk-, and 24% for 52-wk-old rats. The corresponding rates for female rats were 5.3%, 15%, 47%, and 20%. Times between start of exposure and first appearance of tumors were shorter in older rats than in younger rats. Most of the angiosarcomas in exposed rat were highly anaplastic primary tumors of the liver with pulmonary metastases. Results indicate that older rats and female rats are more susceptible to induction of angiosarcomas by VC than younger rats and female rats, respectively. (3 Refs)

25. EFFECT OF ETHANOL ON VINYL CHLORIDE CARCINOGENESIS.

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Environ Health Perspect; 41:59-62 1981

The potential cocarcinogenicity of ethanol with vinyl chloride (VC) was studied in male Sprague-Dawley rats. A total of 320 rats (80 rats in each of four groups) were studied: Group 1 was exposed to VC (600 ppm, 4 hr/day, 5 days/wk for 1 yr), Group 2 was exposed to VC and ethanol (5% in water, beginning 4 wk before the start of VC exposure and continuing for life), Group 3 was exposed only to ethanol, and Group 4 was exposed only to filtered air. At 18 mo rats exposed to VC showed an av weight loss of approx 9%. At 18 mo the survival rate was 40% for Group 1, 18% for Group 2, 73% for Group 3, and 70% for Group 4. Angiosarcomas were found in 23% of Group 1, 50% of Group 2, and 0% of Groups 3 and 4. Hepatocellular carcinomas were found in 44% of Group 1, 60% of Group 2, 10% of Group 3, and 0% of Group 4. Lymphosarcomas were found in all groups but most frequently in Group 2. Endocrine tumors were found in 57 rats in Group 3, compared with 29 in Group 1, 30 in Group 2, and 8 in Group 4. Some rats developed more than one angiosarcoma or carcinoma. Results indicate that ethanol has a strong cocarcinogenic effect in rats exposed to VC. (8 Refs)

26. EFFECT OF PHENOBARBITAL ON THE DEVELOPMENT OF TUMORS IN MICE TREATED NEONATALLY WITH N-ETHYL-N-NITROSOUREA.

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Gan; 73(1):111-114 1982

This study was undertaken to evaluate the effect of phenobarbital on the development of neurogenic tumors induced in mice by neonatal administration of N-ethyl-N-nitrosourea (ENU). A total of 185 A/He mice was divided into four groups. Continuous oral administration of phenobarbital (0.05%) in drinking water was commenced 4 wk after birth in Group I. A single injection of 40 mg/kg of ENU was given subcutaneously on the back within 24 hr after birth in Group II. After neonatal injection of ENU, phenobarbital was commenced 4 wk after birth in Group III. Group IV was the untreated control. The experiment was terminated 12 mo after birth. The serum level of phenobarbital at the end of the experiment was 8.7 ug/ml in Group I and 7.0 ug/ml in Group III. Neurogenic tumors were induced only in groups treated with ENU. The incidence was 5.7% in Group II and 10.9% in Group III, though the difference between the two groups was not statistically significant. A total of three tumors (3.0%) was induced in the central nervous system and five tumors (5.1%) in the peripheral nervous system. Histologically, the former were oligodendroglioma and the latter were schwannoma. Lung tumors, lymphomas and hepatic tumors were also induced by ENU, and in male mice phenobarbital had a suppressing effect on the development of liver tumors. (Author abstract) (19 Ref s)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

27. EFFECTS OF POLYCHLORINATED BIPHENYLS AND ENVIRONMENTAL TEMPERATURE ON IN VITRO FORMATION OF BENZO[A]PYRENE METABOLITES BY LIVER OF TROUT (SALMO GAIRDNERI).

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Biochem Pharmacol; 31(4):561-566 1982

Rainbow trout (Salmo gairdneri) held at 7 C and 16 C were given Aroclor 1254 (PCB) (10 mg/kg body wt) via ip injections. The binding of [3H] benzo[a]pyrene (BaP) to deproteinized salmon sperm DNA was assayed (pmoles BaP equivalents per mg DNA per mg protein) using the post-mitochondrial supernatant (S 10) fractions from livers of fish at 24-168 hr after the PCB exposure. Liver enzymes from the untreated fish acclimated at 7 C yielded an av binding value (0.37 -0.17) which was significantly greater (p less than 0.05) than the value (0.07 -0.03) for untreated fish at 16 C. Liver supernatant fractions from PCB-induced fish acclimated at 16 C and sampled at 24-120 hr showed a substantial increase (p less than 0.05) in the binding (av value 2.4 -1.8) compared to the value obtained with untreated fish at 16 C. At 24, 48 and 120 hr after the PCB treatment of fish held at 7 C, there was no significant increase in the binding value or extent of metabolism of BaP compared to that obtained with the untreated fish at 7 C. However, at 168 hr, three of four fish at 7 C responded to the PCB treatment with significantly (p less than 0.05) increased binding values (3.3 -1.6). Chromatographic analyses of the ethyl acetate-soluble metabolites revealed that 3-hydroxy BaP and 7,8- and 9,10-dihydrodiols were the major metabolites; K-region metabolites were formed in trace amounts in untreated and PCB-treated fish at both temperatures. No marked qualitative differences were observed in metabolite profiles after the PCB treatment; however, overall metabolism of BaP and production of reactive metabolites by liver enzymes were considerably (p less than 0.05) enhanced in the PCB-induced fish at both 7 C and 16 C. (Author abstract) (42 Refs)

28. BINDING OF BENZO[A]PYRENE TO HISTONES AND ALTERED AFFINITY OF MODIFIED HISTONE 1 FOR DEOXYRIBONUCLEIC ACID.

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Biochemistry; 21(4):601-607 1982

The covalent binding of benzo[a]pyrene (B[a]P) to acid-extractable chromosomal proteins and the subsequent effect on histone 1-DNA interaction have been characterized in a model system by utilizing calf thymus nuclei as targets and rat liver microsomes as an exogenous source of enzymes for the metabolic activation of B[a]P. A two-step ion-exchange chromatography and desalting procedure was employed for removing noncovalently bound B[a]P and other contaminants. Fluorography of acetic acid-urea and Triton-acetic acid-urea-polyacrylamide gels indicated that H1 and H3 were the only principal histone targets in [3H]B[a]P-modified calf thymus nuclei. The validity of this assignment was confirmed by comparison of the chromatographic distributions of [3H]B[a]P cpm among peptides derived from the HClO4-soluble (H1) and HClO4-insoluble (core histones) protein fractions to the distributions obtained for authentic individual histone fractions. Comparison of amino acid compositions in individual peptide fractions which bound [3H]B[a]P differentially yielded some insight into the probable target amino acid residues for B[a]P binding. On the basis of electrophoresis in polyacrylamide gels, it appeared as if B[a]P had bound to multiple subfractions of Hl and H3. The equivalent distribution of covalently attached [3H]B[a]P among the major peptides of H1 and H3 modified either in intact nuclei or while free in solution implied that the relative accessibility of major portions of the H1 and H3 molecules for covalent B[a]P binding is not affected by interactions with DNA or other chromosomal proteins. Covalent attachment of [3H]B[a]P to purified H1 reduced the affinity of this histone for DNA-cellulose (Author abstract) (55 Refs)

29. INFLUENCE OF COENZYME A ON THE IN VITRO BINDING OF BENZO(A)PYRENE METABOLITES TO PROTEIN.

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Res Commun Chem Pathol Pharmacol; 35(2):329-332 1982

Incubation of 20,000 x g supernatants of liver homogenates from female Wistar rats with benzo(a)pyrene (BP) and other cofactors in the presence of coenzyme A (CoA) produced metabolites that required extensive hydrolysis successively in 2N NaOH, 2N HC1, 2n NaOH and 6N HC1 for their release. It is suggested that coenzyme A activated benzpyrenyl-amino acid formed via epoxide(s). The activated amino acid(s) became bound to thiol protein. (Author abstract) (6 Refs)

30. EFFECTS OF ESTROGENS ON ARYL HYDROCARBON HYDROXYLASE MEDIATED BINDING OF BENZO(A)PYRENE METABOLITES TO DNA IN VITRO.

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Dept. Biochemistry, Coll. Medicine, Univ. South Florida, Tampa, FL, 33612
Biochem Biophys Res Commun; 104(4):1349-1355 1982

Liver microsomes from mice injected with 0.1 or 2 mg of estradiol (ES) 24 prior to, during and 24 hr after injection of 3-methylcholanthrene (MC), exhibited a significantly decreased capacity to mediate the binding of benzo(a)pyrene metabolites to DNA, compared to microsomes from mice which received only MC. The enzyme and cytochrome components of the aryl hydrocarbon hydroxylase (AHH) were not affected by either ES treatment, suggesting ES may act as a non-competitive inhibitor of AHH activity. (20 Refs)

31. EFFECTS OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF 2-ACETYLAMINOFLUORENE IN THE RAT.

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J Toxicol Environ Health; 9(1):63-76 1982

Effects of selenium on metabolism of 2-acetylaminofluorene (AAF) in male weanling CD rats were investigated. Animals were fed either a diet deficient in Se or the same diet supplemented with 0.5 ppm Se as sodium selenite. Hepatic microsomal metabolism of [9-14C]AAF (1 mCi/millimole) was measured in vitro. Microsomes from Se-deficient rats generated significantly less 3-OH-AAF than those from Se-supplemented animals. Only small amounts of N-OH-AAF were produced and no difference was noted between the two groups of animals. Moderately increased activity of glucuronyltransferase occurred in Se-deficient rats while hepatic soluble sulfotransferase activity was the same in both groups. Se-deficient rats excreted more of the given dose of AAF than did Se-supplemented rats; the increase was due to glucuronic acid- and sulfuric acid-conjugated metabolites and non-ether-extractable, water-soluble metabolites. Se-deficient rats excreted more N-OH-AAF, 7-OH-AAF, and 3-OH-AAF, while Se-supplemented rats excreted more 5-OH-AAF. Se-deficient rats excreted more of the administered dose of AAF as 7-OH-AAF than did Se-supplemented animals. A protective effect of dietary Se against AAF-induced hepatocarcinogenesis may be due in part to the inhibition of N-hydroxy-AAF production in vivo. (45 Refs)

32. EFFECTS OF DIETARY SELENIUM AND VITAMIN E ON COVALENT BINDING OF AFLATOXIN TO CHICK LIVER CELL MACROMOLECULES.

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J Nutr; 112(2):350-355 1982

Day-old single comb white Leghorn chicks of both sexes maternally depleted in selenium (Se) and vitamin E (VE) were fed a low Se and VE-free semipurified basal diet or that diet supplemented with graded levels of Se (0.2-20.0 ppm as Na_2SeO_3) or VE (100 IU/g as all-rac-alpha-tocopheryl acetate), or both. At 14 days of age, chicks were given 1 mg/kg [3H]aflatoxin B1 (AFB1) ip and killed either 2 or 24 hr later. Covalent binding of AFB1 to liver DNA and RNA in chicks fed the basal diet was significantly greater than in chicks supplemented with Se or VE, or both. Phenobarbital treatment prior to administration of AFB1 decreased adduct formation in most groups, and abolished differences in adduct formation due to diet. These results suggest that combined Se-VE deficiency enhances activation or inhibits detoxification of AFB1 in vivo. (Author abstract) (29 Refs)

33. EVIDENCE FOR A CYTOCHROME P-420 CATALYZED MECHANISM OF ACTIVATION OF N-HYDROXY-2-ACETYLAMINOFLUORENE.

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Cancer Biochem Biophys; 5(4):213-217 1981

Cytochromes P-450 and P-420 were solubilized from microsomes from perfused livers of phenobarbital-treated male rats. Electron spin resonance spectroscopy revealed the formation of a nitroxyl radical intermediate in the reaction activating N-hydroxy-2-acetylaminofluorene (N-OH-AAF) in the presence of linoleic acid hydroperoxide. The studies suggest the involvement of the P-450 system in conversion of N-OH-AAF to N-acetoxy-2-acetylaminofluorene and 2-nitrosofluorene, and confirm that the P-420 system, whether naturally occurring in microsomes or induced to form P-420 spin forms, is capable of catalyzing peroxidative type reactions. (18 Refs)

34. EFFECT OF BUTYLATED HYDROXYANISOLE, ALPHA-ANGELICA LACTONE, AND BETA-NAPHTHOFLAVONE ON BENZO(A)PYRENE:DNA ADDUCT FORMATION IN VIVO IN THE FORESTOMACH, LUNG, AND LIVER OF MICE.

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Cancer Res; 42(4):1199-1204 1982

The effects of alpha-angelica lactone (alpha-AL), butylated hydroxyanisole (BHA), and beta-naphthoflavone (beta-NF) on the amount of benzo(a)pyrene (BP) metabolite:DNA adducts formed in the forestomach, lung, and liver of ICR/Ha mice were investigated 48 hr after po administration of BP. BP was administered to mice in amounts known to result in BP-induced neoplasia in certain tissues. Analysis of deoxyribonucleosides by high-pressure liquid chromatography showed that several BP metabolite:DNA adducts were formed in each tissue examined. The major identified adduct in each tissue cochromatographed with the (-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The (-)-7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was detected in each of the tissues. As a percentage of total DNA-associated radioactivity, the BPDEI:DNA and BPDEII:DNA adducts accounted for 14% in the forestomach, 39% in the lung, and 3% in the liver. Another adduct, possibly derived from BP: phenol(s), was detected in lung and liver. Early eluting unidentified DNA-associated radioactivity was also present in each of the tissues and accounted for the majority of the radioactivity (88% in forestomach, 57% in lung, and 97% in liver). Although total DNA-associated radioactivity in liver was approximately 15-fold higher than in lung and 5-fold higher than in forestomach, the specific activities of the BPDEI:adducts and of the BPDEII:adducts were approximately the same in these organs. Addition of alpha-AL or BHA to the diet inhibited BPDEI:DNA adduct formation in the forestomach and liver but not in the lung. The effect of beta-NF was not tissue specific; this aryl hydrocarbon hydroxylase inducer decreased markedly (80 to 90%) BPDEI:DNA adduct formation in all three tissues. The radioactivity associated with the early eluting peaks was also reduced when alpha-AL, BHA, or beta-NF was fed to the mice. The inhibition of BPDEI:DNA and BPDEII:DNA adduct formation by alpha-AL, BHA, and beta-NF is discussed in relation to similar studies where these compounds inhibited BP-induced neoplasia. (Author abstract) (53 Refs)

35. DIFFERENTIAL EFFECTS OF DIETARY BHA ON HEPATIC ENZYME ACTIVITIES AND BENZO[A]PYRENE METABOLISM IN MALE AND FEMALE NMRI MICE.

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Carcinogenesis; 3(1):15-19 1982

The effect of dietary 2(3)-tert-butyl-4-hydroxy-anisole (BHA) alone and in combination with intraperitoneal injections of 3-methylcholanthrene (MC), on hepatic enzyme activities and benzo[a]pyrene (BP) metabolism was compared in male and female NMRI mice. In general, the characteristic induction pattern following dietary BHA administration in female mice could also be seen when male mice were used. The increase in epoxide hydrolase and cytosolic glutathione S-transferase following BHA feeding was however not as pronounced in males as in females. Also, MC treatment appeared to counteract the induction of GST activity by BHA in females but not no such effect in males. Liver microsomes from untreated male mice catalyzed the metabolism of BP less efficiently than did microsomes from females. BHA treatment increased this activity in both sexes to a comparable extent and the overall activity was the same in males and females having received MC. The pattern of BP metabolites was altered following BHA treatment. In general, an increase in BP-4,5-diol and a decrease in 9-OH-BP was observed. This pattern was also noticed when microsomes from MC treated and MC BHA treated animals were compared. MC treatment alone increased the amount of BP-7,8-diol, the quinones and the phenols. The present report indicates that several factors may contribute to the response to dietary BHA in mice. Whether this has any consequence in regard to this compound's anticarcinogenic effect remains to be elucidated. (Author abstract) (32 Refs)

36. METABOLISM AND ACTIVATION OF AFLATOXIN B1 BY RECONSTITUTED CYTOCHROME P-450 SYSTEM OF RAT LIVER.

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Cancer Res; 42(3):1120-1124 1982

Metabolism and activation of aflatoxin B1, a potent hepatocarcinogenic and mutagenic mycotoxin of Aspergillus flavus, were investigated in the reconstituted enzyme system composed of purified NADPH-cytochrome P-450 reductase and cytochrome P-450 or P-448 or rat liver. The aflatoxin M1 formation was strictly mediated by P-448 purified from the liver microsomes of polychlorobiphenyl- and 3-methylcholanthrene-treated rats, while the aflatoxin Q1 formation, as well as the binding to DNA, were catalyzed by both P-450 and P-448. Differences between the kinetic data on metabolism and activation of aflatoxin B1 obtained with the reconstituted cytochrome systems and those obtained with the microsomal and nuclear systems were discussed, and the significance of these biochemical data in the in vivo carcinogenicity of aflatoxin B1 was evaluated. (Author abstract) (37 Refs)

37. FORMATION OF N-(GLUTATHION-S-METHYLENE)-4-AMINOAZOBENZENE FOLLOWING METABOLIC OXIDATION OF THE N-METHYL GROUP OF THE CARCINOGEN, N-METHYL-4-AMINOAZOBENZENE.

Ketterer B, Srai SK, Waynforth B, Tullis DL, Evans FE, Kadlubar FF

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Chem Biol Interact; 38(3):287-302 1982

A major biliary metabolite of the hepatocarcinogen, N,N-dimethyl-4-aminoazobenzene (DAB), in the rat was identified as N-(glutathion-S-methylene)-4-aminoazobenzene (GS-CH2-AB). This conjugate was prepared synthetically by a Mannich condensation of 4-aminoazobenzene (AB), formaldehyde (CH2O) and glutathione (GSH) and has been characterized by chemical analysis and by ultraviolet, visible and 13C-NMR spectroscopy. The same conjugate was also formed in vitro by incubating N-methyl-4-aminoazobenzene (MAB), NADPH, NADH and GSH with rat hepatic microsomes. Evidence is presented that GSH reacted with an intermediate resulting from a cytochrome P-450-dependent oxidation of the N-methyl substituent. This reactive intermediate is presumed to be either an N-methylol or a methimine derivative of AB. The significance of this detoxification mechanism is discussed. The presence of an additional major aminoazo-dye GSH conjugate is also noted. (Author abstract) (31 Refs)

38. A FREE RADICAL MECHANISM FOR ARYLAMINE INDUCED CARCINOGENESIS INVOLVING PEROXIDES.

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Biochem Pharmacol; 31(4):607-608 1982

A 1 e oxidation of N-methyl-4-aminoazobenzene (MAB) catalyzes more binding than the 2 e monooxygenase mechanism in the presence of liver sulfotransferase. Covalent binding of (14C)MAB metabolites to exogenous DNA or microsomal protein demonstrated that hydroperoxide was almost 400x more effective than NADPH in catalyzing the binding. NADPH/reductase may reduce the radical formed by the 1 e oxidation pathway of cytochrome P450. The hydroperoxide catalyzed binding was not affected by addition of cytosol, while the NADPH system was markedly enhanced. Addition of ATP and sulfate further enhanced the cytosol effect, suggesting that the cytosol effect was probably due to sulfotransferase acting on the NOH MAB formed by the 2 e oxidation pathway carried out by microsomal amine oxidase/4. No NOH MAB was formed with hydroperoxide. Cytochrome P450 catalyzed both N demethylation and ring hydroxylation of MAB and the N hydroxylation was catalyzed by microsomal amine oxidase. In dogs and mice, the 1 e pathway of the monooxygenase activity of bladder and lung tissue may be responsible for carcinogenesis in these organs following administration of p-dimethylaminoazobenzene. In mouse liver carcinogenesis, both the 1 e and 2 e pathways should be considered. (9 Refs)

39. IDENTIFICATION OF MUTAGENIC METABOLITES FORMED BY C-HYDROXYLATION AND NITROREDUCTION OF 5-NITROACENAPHTHENE IN RAT LIVER.

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Cancer Res; 42(4):1243-1248 1982

The metabolism of the mutagen and carcinogen, 5-nitroacenaphthene, by the 9,000 x g supernatant from the livers of Aroclor-pretreated rats was studied. The major primary metabolites were 1-hydroxy-5-nitroacenaphthene and 2-hydroxy-5-nitroacenaphthene. These metabolites were oxidized to 1-oxo-5-nitroacenaphthene and 2-oxo-5-nitroacenaphthene, hydroxylated to cis-1,2-dihydroxy-5-nitroacenaphthene and trans-1,2-dihydroxy-5-nitroacenaphthene and reduced to 1-hydroxy-5-aminoacenaphthene and 2-hydroxy-5-aminoacenaphthene. Reduction of 1-and 2-oxo-5-nitroacenaphthene to 1-oxo- and 2-oxo-5-aminoacenaphthene was also observed. When incubations were carried out in a N2-enriched atmosphere (10% O2 in N2), the major metabolites were 1-hydroxy- and 2-hydroxy-5-nitroacenaphthene and 2-oxo-5-aminoacenaphthene. Selected metabolites were tested for mutagenicity toward Salmonella typhimurium TA98. The most mutagenic of the metabolites tested, in the presence or absence of rat liver 9,000 x g supernatant, were 1-hydroxy-5-nitroacenaphthene and 1-oxo-5-nitroacenaphthene. These results indicate that the 9,000 x g supernatant from the livers of Aroclor-pretreated rats is capable of catalyzing both the oxidation and reduction of 5-nitroacenaphthene and that the reduced derivatives of 1-hydroxy- or 2-hydroxy- or 1-oxo- or 2-oxo-5-nitroacenaphthene are proximate mutagens. (Author abstract) (22 Refs)

40. SPECIFICITY OF A PHENOBARBITAL-INDUCED CYTOCHROME P-450 FOR METABOLISM OF CARBON TETRACHLORIDE TO THE TRICHLOROMETHYL RADICAL.

Noguchi T, Fong KL, Lai EK, Alexander SS, King MM, Olson L, Poyer JL, McCay PB
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Biochem Pharmacol; 31(5):615-624 1982

Evidence is presented which demonstrates that the first polypeptide to disappear in liver microsomes of phenobarbital-induced rats treated with CCl4 was the 52,000 dalton P-450 cytochrome. Data are also presented which show that this form of cytochrome P-450 was capable of generating the trichloromethyl radical from CCl4 in a reconstituted system containing the purified cytochrome, NADPH-cytochrome P-450 reductase, NADPH, CCl4, and the spin-trapping agent, phenyl-t-butyl nitrone. Other cytochrome P-450 fractions not containing the 52,000 dalton form did not produce this radical. The formation of this highly reactive radical may have resulted in localized damage to the cytochrome, causing the cytochrome either to be released from the microsomal membrane or to form large aggregates which did not migrate in the gel electrophoretic procedures employed. (Author abstract) (30 Refs)

41. HEPATIC MICROSOMAL METABOLISM AND COVALENT BINDING OF 2,4-DINITROTOLUENE.

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Toxicol Appl Pharmacol; 62(2):325-334 1982

The role of hepatic drug-metabolizing enzymes in the activation and detoxification of 2,4-dinitrotoluene (DNT), the effect of DNT treatment in vivo on hepatic enzyme activities in vitro, and in vitro metabolism and covalent binding of DNT to liver subcellular fractions were investigated. Adult male Fischer-344 inbred albino rats, four animals at each dose level, were treated with 70, 35, and 14 mg DNT/kg body wt by gavage for 5 consecutive days. A significant decrease in microsomal anaerobic nitroreductase activity, and a dose-related increase in liver cytosolic aerobic azoreductase activity were observed at the two higher doses. Treatment with DNT did not appreciably alter the pattern of DNT metabolism in hepatic microsomes or cytosol but did cause a slight increase in the rate of reductive metabolism under anaerobic conditions. No detectable metabolism of DNT occurred in liver microsomes from phenobarbital or Aroclor 1254-treated rats in the absence of NADPH and a regenerating system or with boiled microsomes. Very little covalent binding was detected in microsomes prepared from control or DNT-treated animals. Phenobarbital or Aroclor also markedly increased covalent binding. In microsomes from control and DNT-treated rats, the amount of covalent binding increased 5 to 10-fold as the oxygen concentration of the incubation decreased from 21 to 0%. In incubations performed for 30 min in nitrogen followed by 30 min in oxygen, less binding occurred than in either aerobic or anaerobic conditions alone. The low capacity of liver microsomes to reductively metabolize DNT under aerobic conditions suggested that gut flora are the primary site of reductive metabolism; an interaction between metabolism of DNT in gut flora and in the liver is apparently involved in toxicity. (29 Refs)

42. EFFECT OF STYRENE ON HEPATIC MIXED FUNCTION OXIDASES, GLUTATHIONE CONTENT AND GLUTATHIONE-S-TRANSFERASE ACTIVITY IN RATS.

Das M, Dixit R, Mushtaq M, Srivastava SP, Seth PK
Industrial Toxicology Res. Centre, Mahatma Gandhi Marg, P.O. Box 80, Lucknow-226001, India
Drug Chem Toxicol; 4(3):219-227 1981

Adult male albino rats given 7 consecutive daily doses of styrene at 270, 450, or 900 mg/kg were assayed for changes in their hepatic enzymes on the 8th day. Glutathione was suppressed at the highest dose, while glutathione-S-transferase was suppressed at the middle and highest doses. Both higher doses elevated arylhydrocarbon hydroxylase, aniline hydroxylase, aminopyrine-N-demethylase, and ethylmorphine-N-demethylase. These results implicate styrene as a potential enhancer of polycyclic aromatic hydrocarbon carcinogenicity. (14 Refs)

43. CONSUMPTION OF POISONOUS PLANTS (SENECIO JACOBAEA, SYMPHYTUM OFFICINALE, PTERIDIUM AQUILINUM, HYPERICUM PERFORATUM) BY RATS: CHRONIC TOXICITY, MINERAL METABOLISM, AND HEPATIC DRUG-METABOLIZING ENZYMES.

Garrett BJ, Cheeke PR, Miranda CL, Goeger DE, Buhler DR
Dept. Animal Science, Oregon State Univ., Corvallis, OR, 97331
Toxicol Lett; 10(2/3):183-188 1982

The effects of the carcinogenic plant comfrey (Symphytum officinale), tansy ragwort (Senecio jacobaea), and bracken (Pteridium aquilinum) on the activity of hepatic drug metabolizing enzymes in rats was investigated. Tansy ragwort and bracken increased the activity of glutathione transferase and epoxide hydrolase. Comfrey and alfalfa increased the activity of aminopyrine N-demethylase. Neither bracken nor St. John's wort (Hypericum perforatum) potentiated the toxicity of tansy ragwort as indicated by rat survival time. Apparently no major toxic interaction exists between tansy ragwort and bracken or St. John's wort. (13 Refs)

44. EFFECTS OF DIETARY AROCLOR 1254 AND CYCLOPROPENE FATTY ACIDS ON HEPATIC ENZYMES IN RAINBOW TROUT.

Voss SD, Shelton DW, Hendricks JD
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Arch Environ Contam Toxicol; 11(1):87-91 1982

Combined effects of Aroclor 1254 (PCB) and cyclopropene fatty acids (CPFA) on various hepatic microsomal enzyme activities were determined in rainbow trout during a 15-wk feeding period. The hepatic microsomal enzyme inducing ability of the PCB was more than enough to overcome the mixed function oxidase suppressing activity of the CPFA. Given alone, the PCB increased cytochrome P-450; the effect was maximal by wk 5. The enzymes assayed were ethoxyresorufin-O-deethylase, ethyoxycoumarin-O-deethylase, and benzo(a)pyrene monooxygenase. (28 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

45. NEW DEVELOPMENTS IN THE FIELD OF VIRUSES IN LIVER DISEASE.

Buffet C
Service d'hepatologie et de gastro-enterologie, hopital Bicetre, 78, rue du General-Leclerc, 94270 Kremlin-Bicetre, France
Rev Prat; 31(59):4251-4254 1981

Hepatitis A, the significance of hepatitis B virus (HBV) markers, HBV marker in alcoholics, HBV and carcinogenesis, and non-A, non-B (NANB) hepatitis virus are discussed. HBV antigens and antibodies (antibodies to HBV surface and core antigens and those related to viral replication) are discussed in relation to the diagnosis of hepatitis B. HBV markers are elevated in alcoholic populations (40%) as compared with normal blood donors (10%). In most alcoholics, HBV markers indicative of former, non-developing HBV infection are observed. The role of HBV in cirrhosis is discussed. Integration of HBV DNA in the cellular genome of hepatoma tissue has been demonstrated. Epidemiologically, geographic zones with a high incidence of hepatitis are strictly superimposable over zones with a high incidence of hepatomas. Patients positive for HBV antigens with or without cirrhosis show a higher incidence of liver neoplasms. Although other factors are involved in tumorigenesis in the liver, HBV is directly involved in the development of hepatomas. Identification, transmission, and characteristics of NANB hepatitis virus and resultant infection are described. (13 Refs) (In FRE)

46. HEPATIC CANCER AND NON-A NON-B TYPE HEPATITIS.

Shibasaki K, Soga K, Honma A, Ichida F
Dept. Internal Medicine, Nippon Dental Coll. Niigata Dental Sch., Niigata, Japan
Nippon Rinsho; 39(10):3251-3256 1981

Patients with chronic hepatic disease included two groups according to presence or absence of hepatitis B surface (HBs) antigen. Hepatic cancer patients with continuous infection of hepatitis B virus (HBV) were classified B-type hepatocarcinoma, and those with non-A non-B (NANB)-type hepatitis were classified NANB type hepatic cancer. Characteristics of the groups were compared. HBs antigens were detected with the aid of RPHA method in 63/125 patients with chronic hepatitis, 33/129 with cirrhosis, and 57/114 with hepatic cancer. Examination of HBV related antigens and antibodies in the serum of 101 patients with hepatic cancer showed that 60/101 had continuous HBV infection, 31/101 had temporary HBV infection, and 10/101 had no detectable HBV antigens or antibodies. Studies of 129 patients with cirrhotic changes indicated that a higher rate of the patients with HBs antigens developed primary hepatic cancer than did those without HBs antigens. Other studies indicated that hepatic cancer occurred within a shorter period of time in patients with presence of HBs antigen than in those without HBs antigen. Comparison of characteristics of B-type hepatocarcinoma patients (B Group) and NANB-type hepatocarcinoma patients (NANB Group) showed that the B Group patients developed cancer with an average of 5 yr earlier than the NANB Group patients, the male:female ratio of the B Group was less than that of the NANB Group, more NANB Group patients had a history of blood transfusions and hepatitis, and more B Group patients had no history of alcohol consumption. (29 Refs) (In JPN)

47. DETECTION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA TISSUES.

Goudeau A, Maupas P, Coursaget P, Drucker J, Chiron JP, Denis F, Diop Mar I, N'Diaye PD
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:77-87 1981

A serological and pathological immunofluorescence study of hepatitis B (HBV) antigens was conducted on liver tissues obtained from 15 patients who died from primary hepatocellular carcinoma (PHC) in Dakar, Senegal, where PHC is obvious upon clinical examination and prevalent in patients in the 30-40 yr age range. Tissue localization of hepatitis B surface antigen and hepatitis B core antigen suggested the following etiological scheme for the HBV role in the genesis of PHC: hepatitis with inflammatory phenomena and necrosis followed by post-necrosis cirrhosis with fibrosis and voluminous regenerative nodules; and PHC evolving from the post-necrotic regenerative nodules. (20 Refs)

48. HEPATOCELLULAR CANCER IN SOUTHERN AFRICAN BLACKS: HBEAG, ANTI-HBE, IGM-ANTI-HBC AND OTHER MARKERS OF HEPATITIS B.

Kew MC, Desmyter J, De Groote G, Frosner G, Roggendorf M, Deinhardt F
(c/o Desmyter) Rega Inst., Catholic Univ. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium
Prog Med Virol; 27:41-48 1981

Using radioimmunoassay, frequency of HBeAg in 98 HBsAg-positive Southern African miners with hepatoma was similar to that in HBs-Ag-positive controls (13 vs 12%). Anti-HBe was slightly less prevalent in patients (60 vs 85%). Anti-HBs was much less prevalent, and anti-HBe and anti-HBc were more prevalent in 50 HBsAg-negative patients than in HBsAg-negative controls. HB markers were found in 88% of HBsAg-negative hepatoma cases and in 70% of HBsAg-negative controls; and in 96% of all hepatoma cases, vs 74% in the control population. All differences are significant. With a single exception, anti-HBe was found only in the presence of anti-HBc. IgM-anti-HBc was found much more frequently in HBsAg-positive patients than in the other groups. (Author abstract) (6 Refs)

49. HEPATITIS B VIRAL MARKERS IN PATIENTS WITH CHRONIC HEPATITIS AND WITH PRIMARY HEPATOCELLULAR CARCINOMA IN TAIWAN.

Tong MJ, Chien MC, Lo KJ, Tsai YT, Lee JK
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:60-65 1981

Three prospective studies on the relationship between hepatitis B viral markers and primary hepatocellular carcinoma (PHC) were conducted with patients of Chinese origin at two veterans hospitals. The frequencies of hepatitis B surface antigen (HBsAg) and anti-HBs were determined in 94 chronic hepatitis patients, and the patients' progress was followed for 3 yr. Hepatitis B viral markers were measured by radioimmunoassay in a study involving 102 patients with PHC and HBsAg and anti-HBs were determined in patients with acute viral hepatitis (40), chronic hepatitis (161), and PHC (126). (6 Refs)

50. A CASE/CONTROL STUDY OF HEPATITIS B VIRUS SEROLOGIC MARKERS IN SENEGALESE PATIENTS SUFFERING FROM PRIMARY HEPATOCELLULAR CARCINOMA.

Coursaget P, Maupas P, Goudeau A, Chiron JP, Raynaud B, Drucker J, Barin F, Denis F, Diop Mar I, Diop B
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-3700 Tours, France
Prog Med Virol; 27:49-59 1981

At least one hepatitis B virus (HBV) marker associated with HBV infection was found in all patients with primary hepatocellular carcinoma (PHC) and in 87-92% of individuals in three control groups (urban Senegalese, rural Senegalese, leprosy patients with known high incidence of HBV infections). In PHC patients, HBV replication occurred 5x more frequently than in controls, and markers of past infection were 2x less frequent. A significant decrease in HBV replication markers was found in the sequence beginning with HBV to cirrhosis and finally to PHC, suggesting that active replication becomes increasingly defective with advancing malignancy. (28 Refs)

51. HEPATITIS B INFECTION IN ALCOHOLIC LIVER DISEASE AND PRIMARY HEPATOCELLULAR CARCINOMA IN FRANCE.

Goudeau A, Maupas P, Dubois F, Coursaget P, Bougnoux P
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:26-34 1981

The prevalence of hepatitis B virus (HBV) markers was studied in 125 asymptomatic heavy drinkers, 163 patients with alcoholic cirrhosis, and 46 patients with histologically proven primary hepatocellular carcinoma. Hepatitis B surface antigen, anti-hepatitis B surface antigen, and anti-hepatitis B core antigen were tested by solid phase radioimmunoassay. Percentages of HBV markers in the three groups were, respectively, 31.2, 54.6, and 21.7, compared to 5% in a control group of 10,000 normal blood donors from the same area in France. (24 Refs)

52. LOCALIZATION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA.

Nazarewicz-de Mezer T, Slusarczyk J, Krawczynski K, Nowoslawski A
Dept. Immunopathology, Natl. Inst. Hygiene, ul. Chocimska 24, 00-791 Warsaw, Poland
Prog Med Virol; 27:66-76 1981

Studies on the localization of hepatitis B (HBV) antigens by immunofluorescence or immunoperoxidase staining or by fluorochrome- or enzyme-labeled antibodies in cells of patients with hepatocellular carcinoma (HCC) are reviewed. All data obtained by immunomorphological analysis of HCC tissue and indicative of a decreasing potential of expression of HBV antigen with increasing malignancy are compatible with the hypothesis on the oncogenic properties of HBV. (50 Refs)

53. INDUCTION OF GAMMAGLUTAMYLTRANSPEPTIDASE-POSITIVE ALTERED HEPATOCYTIC LESIONS BY COMBINATION OF TRANSPLACENTAL-INITIATION AND POSTNATAL-SELECTION.

Ogawa K, Yokokawa K, Tomoyori T, Onoe T
Dept. Pathology, Sapporo Medical Coll., Sapporo 060, Japan
Int J Cancer; 29(3):333-336 1982

The purpose of this study was to induce in postnatal life the selective growth of altered hepatocytic populations which had been induced in utero by various chemicals. Pregnant rats of a Wistar strain were given a single dose of various chemical carcinogens on the 18th gestational day. From 2 mo postpartum, both the mothers and offspring were given a diet containing 2-acetylaminofluorene (2-AAF) at a concentration of 0.02% for 2 wk. Then, at the end of the 1st wk after the 2-AAF feeding, a two-thirds partial hepatectomy was performed. All the animals were killed 1 wk after the partial hepatectomy and were examined for the incidence of gamma-glutamyltranspeptidase (GGT)-positive altered hepatocytic foci in the liver. The transplacental administration of not only a hepatic carcinogen, diethylnitrosamine (DEN) but also 7,12-dimethylbenzanthracene (DMBA), which does not usually produce hepatocellular carcinomas in adult rats, induced GGT-positive altered hepatocytes in the liver of the offspring. These hepatocytes grew into grossly visible hyperplastic nodules within a wk after the two-thirds partial hepatectomy. The possible applicability of the transplacental initiation-postnatal selection model for the short-term assay of transplacental carcinogenicity is discussed. (Author abstract) (21 Refs)

54. DISTRIBUTION OF NOVIKOFF ASCITES HEPATOMA ANTIGENS P39 AND P49 IN VARIOUS TUMORIGENIC CELL LINES.

Schmidt WN, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Cancer Center, Nashville, TN, 37232
Cancer Res; 42(4):1441-1445 1982

This study investigates the specificity of two antigenic proteins with mol wt of 39,000 and 49,000 respectively (p39 and p49), present in Novikoff ascites hepatoma. Chromatins and cytosol fractions were assayed from a number of tumorigenic cell lines by identifying antigenic species immunologically on nitrocellulose transfers containing proteins separated electrophoretically. Immunoreactivity was confirmed with complement-fixation. Although the p49 antigen was present only in Novikoff ascites hepatoma and a tissue culture line derived from these ascites cells, the p39 antigen was found in every carcinoma cell line examined. In contrast, neither antigen was present in a representative sarcoma, fibrosarcoma, or Walker 256 carcinosarcoma. These results suggest that the p39 antigen is a protein specific for malignant cells derived from the epithelium. The overall expression of the p39 antigen by the various cell lines examined did not appear to be influenced by in vivo or in vitro growth of homologous cell lines. This latter feature suggests that the p39 antigen is a stable, possibly structural component of neoplastic cells. (Author abstract) (29 Refs)

55. DETECTION OF HEPATITIS B VIRUS DNA SEQUENCES IN HUMAN HEPATOCELLULAR CARCINOMA IN AN INTEGRATED FORM.

Brechot C, Pourcel C, Louise A, Rain B, Tiollais P
(c/o Tiollais) Unite de Recombinaison et Expression Genetique, INSERM U 163, Institut Pasteur, 28 Rue du Dr. Roux, F-75724 Paris Cedex 15, France
Prog Med Virol; 27:99-102 1981

The state of viral sequences in human hepatocellular carcinoma (HCC) and human hepatoma cell line (PLC/PRF/5) was analyzed by blot-transfer hybridization with cloned DNA as a probe. Hepatitis B virus (HBV) DNA sequences, both undigested and digested by EcoRI and HindIII endonucleases, were studied by agarose gel electrophoresis. HBV DNA sequences were integrated into the cellular DNA of the three tumor tissues and the hepatoma cell line, providing additional evidence for the causal relationship between HBV chronic infection and HCC. (13 Refs)

56. TRANSCRIPTS OF CELLULAR ANALOG OF VIRUS SARCOMA SRC GENE IN MOUSE LIVER.

Mett VL, Chumakov IM, Kiselev LL
Inst. Molecular Biology, Moscow, USSR
Dokl Akad Nauk SSSR; 261(6):1471-1472 1981

Analysis of the expression of protosarc gene in the liver of mice uninfected with Moloney sarcoma virus (MSV) showed synthesis of poly(A)-RNA homologous to RNA of MSV. Poly(A)-RNA showing hybridization with src gene of MSV were also detected in the liver of mice treated with the hepatocarcinogen o-aminoazotoluene. These findings can indicate transcription of the endogenous sarcoma provirus during chemical carcinogenesis. (7 Refs) (In RUS)

57. PLASMA ALPHA-FETOPROTEIN ELEVATION AND MUTAGENICITY OF URINE AS EARLY PREDICTORS OF CARCINOGENICITY IN BENZO(A)PYRENE FED RATS.

Boyd JN, Misslbeck N, Babish JG, Campbell TC, Stoewsand GS
Dept. Food Science and Technology, Cornell Univ., New York State Agricultural Experiment Station, Geneva, NY, 14456
Drug Chem Toxicol; 4(3):197-205 1981

Weanling male Fischer rats were fed on diets containing benzo(a)pyrene (BaP) at (a) 0 or 1,000 ppm or (b) 0, 1, or 100 ppm for 11 wk on diet (a) or 8 wk on diet (b). Some of the animals' diet contained 500 ppm sodium phenobarbital (PB) for the last 5 wk (none getting 1,000 ppm BaP). Cardiac blood was obtained weekly at wk three and assayed for alpha-fetoprotein (AFP). Hepatic slices were obtained at wk six and stained for gamma-glutamyl transpeptidase (GGT) activity. Also at wk six 8-hr urine samples were taken and assayed by the Salmonella/mammalian microsomal test with S typhimurium strain T98. The AFP level was independent of all diets except for notable elevation at wk six in the 1,000 ppm BaP animals. Except for 1,000 ppm BaP animals assay for GGT was independent of other variables. The mutagenesis assay was positive only for the 1,000 ppm BaP animals at wk six with and without activation, and for the 100 ppm BaP with PB animals at wk eight with activation. The AFP and urinary mutagenesis assays were recommended as co-tests for short term carcinogenicity potential evaluation. (12 Refs)

58. ULTRASTRUCTURAL LOCALIZATION OF ALPHA-FETOPROTEIN SYNTHESIS IN REGENERATING LIVER.

Baranov VN, Engel'gardt NV, Lazareva MN, Gusev AI

Lab. Cell Pathology and Electron Microscopy, Inst. Human Morphology, Moscow, USSR

Biull Eksp Biol Med; 91(12):736-738 1981

The electron microscope immunoperoxidase technic was used for the localization of alpha-fetoprotein (AFP) synthesis in regenerating liver of SWR mice. Liver regeneration was induced by exposure to carbon tetrachloride vapors. AFP was detected in very few hepatocytes adjacent to the zone of necrosis. AFP was present in the perinuclear space, and on the membranes and ribosomes of Golgi apparatus. (15 Refs) (In RUS)

59. SERUM FERRITIN AND BINDING OF SERUM FERRITIN TO CONCANAVALIN A AS A TUMOR MARKER IN PATIENTS WITH PRIMARY LIVER CELL CANCER AND CHRONIC LIVER DISEASE.

Chapman RW, Bassendine MF, Laulicht M, Gorman A, Thomas HC, Sherlock S, Hoffbrand AV

Dept. Medicine, MRCP, Pond St., London, NW3 2QG, England

Dig Dis Sci; 27(2):111-116 1982

Total ferritin concentration was measured in sera of 30 patients with primary liver cell cancer (PLCC) and 33 patients with cirrhosis and compared with serum alpha-fetoprotein levels as a diagnostic marker of PLCC. Serum ferritin concentration was raised in 19 patients (63%) with PLCC and 11 patients (33%) with cirrhosis. The median level was significantly higher (p less than 0.001) in the PLCC group (560 ug/liter) than in the cirrhotic group (137 ug/liter), although there was considerable overlap. Serum ferritin was positively correlated with serum aminotransferase levels in the cirrhotic patients ($r = 0.53$, p less than 0.001), reflecting hepatic necrosis, but not in the PLCC patients. The concentration of ferritin binding to concanavalin A was measured in the sera of patients with elevated total serum ferritin. Although the proportion of bound ferritin was decreased in the majority of PLCC sera compared to controls (p less than 0.001), there was overlap with the cirrhotic group, making it unlikely that this assay is useful in distinguishing a tumor-specific isoferritin. Serum alpha-fetoprotein levels were elevated in 21 patients (70%) with PLCC and proved to be a highly sensitive and specific test for PLCC. There was no relationship between the alpha-fetoprotein and serum ferritin concentrations. Serum ferritin is inferior to alpha-fetoprotein as an initial screening test for PLCC, but in alpha-fetoprotein-negative patients serum ferritin may have a role in monitoring therapy. Patients with cirrhosis with normal serum alpha-fetoprotein and ferritin concentrations are very unlikely to have PLCC. (Author abstract) (20 Refs)

60. IMMUNOLOGICAL DETECTION OF SPHINGOMYELIN-CARRYING PROTEIN IN TUMORS AND IN EMBRYONAL RAT LIVER.

Diatlovitskaia EV, Sinitsyna EV, Timofeeva NG, Iakimenko EF, Kuprina NI, Bergel'son LD

M. M. Shemiakin Inst. Bioorganic Chemistry, Moscow, USSR

Biokhimiia; 47(1):62-65 1982

The presence of sphingomyelin-carrying protein (SCP) was studied in the cytosol of hepatoma 27, sarcoma 45, Jensen sarcoma, nephroma RA, and in the normal, regenerating, and embryonal rat liver. SCP was assayed by double immunodiffusion technic. SCP was detected in the postmicrosomal supernatant of all tumors tested. SCP was also present in the embryonal liver. SCP was not detected in the normal and regenerating liver, or in the blood of tumor-bearing rats. (16 Refs) (In RUS)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

61. ELECTRON MICROSCOPIC OBSERVATIONS OF HEPATIC AND SUBCUTANEOUS HEMANGIOSARCOMAS INDUCED IN MICE EXPOSED TO VINYL CHLORIDE MONOMER.

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Am J Ind Med; 2(2):103-117 1981

Neoplastic effects of vinyl chloride was studied in mice in short exposure (4 wk) to low doses (1, 10, 100, 300, and 600 ppm). A mouse of the 10 ppm group developed a subcutaneous hemangiosarcoma, 29 wk after exposure. Histologically the tumor was localized in the subcutaneous connective tissue of the ear, and formed blood channels that appeared to be freely communicated. Neoplastic cells (NC) that directly lined the blood cavities were generally attenuated. Focal necrosis, hemorrhage, and hemosiderin deposition were observed. Ultrastructure of the attenuated NC was similar to that of capillary endothelium in the connective tissue. A mouse of the 600 ppm group developed an hepatic hemangiosarcoma approx 65 wk after exposure. The tumor was found on the surface of the lobe of the liver, and in addition, multiple pulmonary tumors were observed. The hepatic tumor showed formation of cystic blood channels, and the stroma of the tumor was frequently sclerotic. Neoplastic tissue contained degenerated hepatic parenchyma. NC lining the blood cavity were attenuated compared with normal sinusoidal endothelium. Pericyte-like cells were characterized by the presence of pinocytotic vesicles and dense bodies beneath the cell membrane. Und er normal conditions the pericyte does not exist in Disse's space of the mouse. Alveologenic tumors were induced at high rate in mice 12 wk and longer after exposure; 23/24 mice in the 600 ppm group, 12/19 in the 300 ppm, 7/16 in the 100 ppm, 3/20 in the 10 ppm group, and in 2/38 control group. (28 Refs)

62. CLASSICAL SYNDROMES IN OCCUPATIONAL MEDICINE: PATHOLOGICAL LESSONS FROM VINYL CHLORIDE ANGIOSARCOMA.

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Am J Ind Med; 2(2):187-196 1981

Similarities in the evolution of the various stages of vinyl chloride (VC)-induced hepatic lesions in man and experimental animals are discussed. The initial lesion in man and rodents is focal proliferation of hepatocytes which show variations in size and appearance of nuclei. Increase of perisinusoidal collagen fibrils and of fat-storing interstitial cells, precursors of fibroblasts, is present. Silver impregnation visualizes the increase of reticulin fibers in circumscribed zones. The precursor lesions do not exclude the simultaneous presence of fully developed angiosarcoma (AS) in other parts of the liver. Diagnostic follow-up by radionuclide scanning, angiography, and subsequent confirmation by open liver biopsy are indicated. The proliferation of sinusoidal cells becomes more conspicuous in both man and animals, and cells with hyperchromatic spindle-shaped nuclei gradually exceed the other sinusoidal cells in number. Intralobular AS is always multicentric in rodents. Exposure of newborn rats produced mainly hepatocellular carcinoma. Trabecular AS is the more frequent form. Increased connective tissue and AS cells which invade the cords are present leading to atrophy and disappearance of hepatocytes. Solid nodules of AS often form. In humans all forms of AS are almost always multicentric discouraging surgical intervention even at early stages. VC produces a well defined histological sequence in animals and man,leading to control of exposure and avoidance of additional disease. (36 Refs)

63. PRIMARY CULTURE OF PRENEOPLASTIC HEPATOCYTES FROM RATS TREATED WITH 2-ACETYLAMINOFLUORENE AND CLOFIBRATE: RELATIONSHIP BETWEEN RESISTANCE TO DIMETHYLNITROSAMINE AND RESPONSIVENESS OF PEROXISOMES.

Sawada N, Furukawa K, Gotoh M, Mochizuki Y, Tsukada H

Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan

Gan; 73(1):1-6 1982

Hepatocytes of 2-acetylaminofluorene-induced hyperplastic nodules of rats treated with clofibrate were transferred to primary culture after dispersion by a collagenase perfusion technique. After 48-hr treatment with dimethylnitrosamine (DMN), the resistance to the agent of the cells forming rod-shaped peroxisomes was examined. Catalase activity of the DMN-resistant cells was also determined. At c oncentrations of 10(-3) M and 10(-4) M DMN, the resistant cell population of hepatocytes with rod-shaped peroxisomes was larger than that of the cells without abnormal peroxisomes. On the other hand, the catalase activity of the attached cells that remained after DMN treatment decreased as the concentration of DMN was increased. The cells showing a stronger induction of the enzyme activity were found to be more sensitive to the cytotoxicity of DMN and they became detached from the culture dishes. (Author abstract) (21 Refs)

64. MATRICAL INCLUSIONS OF PEROXISOMES INDUCED BY CLOFIBRATE IN PRENEOPLASTIC HEPATOCYTES OF RATS FED 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE.

Gotoh M, Mochizuki Y, Sawada N, Tsukada H
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan
Gan; 73(1):7-13 1982

The response of peroxisomes to clofibrate in preneoplastic hepatocytes of rats fed 3'-methyl-4-dimethylaminoazobenzene was examined histochemically (using the 3,3'-diaminobenzidine reaction) and electron microscopically. Morphometrical examinations revealed that the number of peroxisomes correlated well with the intensity of the histochemical reaction. Preneoplastic hepatocytes which responded to clofibrate with a marked proliferation of peroxisomes showed no matrical inclusions or merely matrical plates in very low incidence in the proliferated peroxisomes. The cells that exhibited a moderate proliferation of peroxisomes showed formation of peroxisomal matrical inclusions in high incidence. The inclusions were matrical plates and tubules showing the same fine structures as those found in 2-acetylaminofluorene carcinogenesis. These peroxisomal inclusions were absent in the cells which responded to clofibrate with no or only a slight increase in the number of peroxisomes. It is suggested that these varieties of peroxisomal changes might reflect the progress of preneoplastic phases of the cells. (Author abstract) (11 Refs)

65. EFFECTS OF PROLONGED ORAL TREATMENT WITH N-FLUOREN-4-YLACETOHYDROXAMIC ACID ON RAT LIVER FINE STRUCTURE.

Flaks B, Yost Y, Flaks A
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Carcinogenesis; 3(1):103-109 1982

Inbred male Leeds strain rats were given a diet containing 0.05% N-fluoren-4-ylacetohydroxamic acid for up to 7 mo. A modified method for the synthesis of this compound is described. Rats were killed at intervals during and after treatment and their liver tissues examined by light and electron microscopy. The treated rats developed a very low incidence of (nonhepatic) tumors and hepatic clear cell foci appeared during the late stages of the experiment. The only significant fine structural changes observed were glycogenosis and alterations in the morphology of the rough endoplasmic reticulum, both of which developed only after prolonged treatment and affected a minority of hepatocytes. These changes are discussed in relation to the fine structural changes elicited by the strongly carcinogenic N-fluoren-2-ylacetamide and the non-carcinogen, N-fluoren-4-ylacetamide. (Author abstract) (29 Refs)

66. DEMONSTRATION OF INJURED HEPATOCYTES AFTER CARBON TETRACHLORIDE ADMINISTRATION BY LOSS OF HISTOCHEMICAL GLUCOSE-6-PHOSPHATASE REACTION.

Kanamura S, Kanai K, Asada-Kubota M
Dept. Anatomy, Kansai Medical Univ., Fumizono-cho 1, Moriguchi 570, Osaka, Japan
Exp Pathol; 20(1):68-70 1981

Histochemical study of thin sections of liver from mice 1.5 hr after sc injection of carbon tetrachloride (0.15 ml/100 g) revealed normal ultrastructure in cells with moderate to abundant amounts of glucose-6-phosphatase (G6Pase). Cells with no G6Pase showed injury in the form of diffusely vesiculated endoplasmic reticulum and sometimes partial distortion of the outer membrane of the nuclear envelope. (7 Refs)

67. HEPATOCYTES WITH EXTRAPEROXISOMAL CATALASE IN RATS FED 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE.

Gotoh M, Mochizuki Y, Furukawa K, Sawada N, Tsukada H
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan
Gan; 73(1):14-20 1982

Histochemical and cytochemical studies were done to further characterize the preneoplastic hepatocytes with extraperoxisomal catalase (EPC-cells) that were found in the livers of rats fed 3'-methyl-4-dimethylaminoazobenzene. Catalase activity was demonstrated cytochemically to be localized in nuclear matrices, hyaloplasm, and peroxisomal matrices of EPC-cells. It is suggested that an impairment of peroxisome formation is involved in the altered intracellular distribution of catalase. Administration of clofibrate increased the catalase activity in EPC-cells. To examine the preneoplastic nature of EPC-cells, activities of glucose-6-phosphatase (G6Pase) and gamma-glutamyl transpeptidase (GGT) were examined, since changes in the activities of these enzymes have been used as markers of putative preneoplastic cells. In the present study, neither weak G6Pase activity nor positive GGT activity was considered to be a consistent feature of EPC-cells. However, available evidence suggests that EPC-cells are one of the carcinogen-induced cell populations with altered phenotypes. (Author abstract) (16 Refs)

68. EFFECT OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND PHENOBARBITAL ON THE OCCURRENCE AND DISTRIBUTION OF FOUR CYTOCHROME P-450 ISOZYMES IN RABBIT KIDNEY, LUNG, AND LIVER.

Dees JH, Masters BS, Muller-Eberhard U, Johnson EF
Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
Cancer Res; 42(4):1423-1432 1982

The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and of phenobarbital (P B) on the distribution and occurrence of four cytochrome P-450 isozymes, Forms 2, 3, 4, and 6, in the kidney, lung, and liver of adult male rabbits was investigated using immunofluorescence. In the kidney, Forms 2 and 3 were localized in the proximal tubules of both untreated and PB-treated animals, while antibodies to Forms 4 and 6 showed weak to negative staining. In TCDD-pretreated animals, Forms 4 and 6 appeared in the renal endothelium, in addition to staining the proximal tubular epithelium intensely. Form 2 was the only isoenzyme of those studied found to be present in the lungs of normal and PB-treated rabbits; it was also present in lungs of TCDD-pretreated rabbits. Form 3 was not detected in any of the rabbit lungs examined. Forms 4 and 6, while not apparent in the lungs of normal or PB-treated animals, were found in the lungs of TCDD-treated animals and also appeared in the endothelium of the pulmonary arteries and veins. All forms tested were present in control liver. The staining for Form 2 was intense in the livers of PB-pretreated animals, as was the staining for Forms 4 and 6 in the livers of TCDD-pretreated animals. Our results indicate that, while PB altered the intensity of staining for Form 2 in the liver and kidney, TCDD altered both the staining intensity and distribution of the isozymes in kidney, lung, and liver, producing, for example, a localization of Forms 4 and 6 in the endothelium of both the kidney and lung which was not seen in either untreated or PB-pretreated rabbits. (Author abstract) (48 Refs)

69. MICROSCOPIC DERIVATIVE CYTOSPECTROPHOTOMETRY.

Liu H, Wang Z, Wang F, Zhang Z
Hebei Medical Coll., Shijrazhuang, People's Republic of China
Zhonghua Wuliyixue Zazhi; 3(2):100-102 1981

A cytospectrophotometric technic is described for DNA analysis. Cells for rat liver cancer induced by diethylnitrosamine and those from normal liver were stained with Feulgen stain and their nuclear DNA was determined at 608-620 nanometer. The av nuclear DNA concentration in liver cancer cells was 15.31 3.40 while that in normal liver cells was 8.91 1.38. The difference was significant. Possible use of this difference in the automatic computerized cytodiagnosis of liver cancer is discussed. (2 Refs) (In CHI)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

70. DISTRIBUTION AND SPECIFICITY OF SEQUENCES IN POLYADENYLATED NUCLEAR RNA OF NORMAL, REGENERATING, AND NEOPLASTIC LIVER.

Fausto N, Schultz-Ellison G, Atryzek V, Goyette M
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
J Biol Chem; 257(5):2200-2206 1982

We determined the homology between nuclear RNA of normal liver and that of regenerating and neoplastic livers. Because of the very low representation of the rare class of sequences (1 copy per cell or less) in liver nuclear RNA, very high RNA/cDNA ratios (as high as 1 x 10(5)) were general ly necessary to obtain maximal levels of hybridization. Complementary DNA prepared from 16-hr regenerating liver polyadenylated nuclear RNA hybridized to the same extent with its homologous RNA and with polyadenylated nuclear RNA isolated from normal liver. We prepared, through several cycles of hybridization, a cDNA probe enriched for regenerating liver polyadenylated nuclear RNA sequences. Hybridization reactions with this enriched probe demonstrated marked differences in the abundance of classes of transcripts between nuclear RNA of normal and regenerating liver. However, the data do not support the view that there is a group of nuclear RNA sequences which is present in regenerating but not in normal liver. Hybridization reactions with cDNA prepared from livers with primary tumors indicated that polyadenylated nuclear RNA from those livers differs markedly from normal liver nuclear RNA in the distribution of its sequences. We conclude that the changes in the rare sequences of polyadenylated nuclear RNA during liver regeneration result from alterations in the abundance of some RNA sequences which are present in normal liver. The same conclusion applies to nuclear RNA of livers with primary tumors but in this case it was not possible to exclude the possibility that 'tumor-specific' nuclear RNA sequences might exist. (Author abstract) (32 Refs)

71. STUDIES ON THE ACTIVITY OF ALPHA-FETOPROTEIN GENE.

Choi NH, Higashi T
Dept. Biochemistry, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Chem Pharm Bull (Tokyo); 29(11):3311-3319 1981

Purified alpha-fetoprotein (AFP) messenger (m)RNA from rat AH-66 hepatoma cells formed complementary (c)DNA upon incubation in a system with avian myeloblastosis virus RNA-dependent DNA polymerase. The (3H)cDNA had a peak fraction of about 1,000 nucleotide length upon alkali-sucrose gradient centrifugation; AFP cDNA hybridized with AFP mRNA, but not with rat liver catalase mRNA. Thermal denaturation analysis showed a sharp melting profile, indicating a faithful transcription in AFP cDNA:mRNA hybrids. The conformation of the AFP gene was studied by digestion of nuclei of AH-66 cells and rat liver cells with DNAse I or microsomal nuclease. Chromosomal proteins (CP) extracted from chromatin of AH-66 and rat liver cells were similar in comparisons by QAE-Sephadex A-25 chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. RNA transcripts from intact and reconstituted chromatin of AH-66 cells hybridized with AFP cDNA, but those from rat liver cells did not, indicating that AFP gene is active in AH-66 cells, but suppressed in liver cells. The addition of one of the fractions of AH-66 CP during reconstitution of rat liver chromatin lead to transcription of the AFP gene; no rat liver CP could be found that when added during reconstitution would inhibit transcription of AH-66 AFP gene. (24 Refs)

72. ISOLATION OF ALPHA-FETOPROTEIN MESSENGER RIBONUCLEIC ACID FROM AH-66 ASCITES HEPATOMA CELLS.

Choi NH, Higashi T
Dept. Biochemistry, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan
Chem Pharm Bull (Tokyo); 29(11):3305-3310 1981

The messenger (m)RNA for alpha-fetoprotein (AFP) was isolated from polysomes of AH-66 rat hepatoma cells by extraction of immunoprecipitates and purification by affinity chromatography with oligo(deoxythymidine)-cellulose column. Sodium dodecyl sulfate polyacrylamide gel electrophoresis of AFP gave two mol wt peaks of 72,000 and 74,000; the purified AFP contained 1.5% hexose, 1.5% hexosamine, and 0.9% sialic acid. Electrophoresis of purified AFP mRNA on acid-urea agarose gel suggested a mol wt of 2,700. Purified anti-AFP antibody from anti-rat AFP horse antiserum was reactive against AH-66 ascites fluid, purified rat AFP, and anti-horse IgG rabbit antibody, but not adult rat serum. A quantitative analysis showed that the molar ratio of anti-AFP antibody to rat AFP is approx one at the equivalent point. Purified AFP mRNA translated in the wheat germ S-30 cell-free system was measured by radioactivity incorporated in immunoprecipitates; results indicated that the obtained AFP mRNA was at least 75% pure in terms of messenger activity. (21 Refs)

73. ACUTE EFFECTS OF SELECTED HEPATOTOXIC AGENTS ON POLYRIBOSOMES AND PROTEIN SYNTHESIS IN THE LIVERS OF RATS FED PURIFIED DIETS CONTAINING HEPATOCARCINOGENS.

Sidransky H, Verney E
Dept. Pathology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Mol Pathol; 36(1):72-85 1982

This investigation was concerned with the effects of certain hepatocarcinogens ingested for long- or short-term intervals upon selected responses of rat liver to specific hepatotoxic stimuli. Rats fed ad libitum for long (3 to 45 wk) periods or force-fed for short (3 days) periods purified diets containing a single hepatocarcinogen, ethionine, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, or thioacetamide, were subjected to the acute administration of a single hepatotoxic agent, such as puromycin, actinomycin D, sparsomycin, hypertonic NaCl or CCl4, and hepatic protein synthesis (in vitro) and polyribosomal aggregation were evaluated. Relating to in vitro protein synthesis, in long-term experiments, puromycin induced less inhibition in the experimental groups than in the control (basal diet) group; and actinomycin D inhibited all groups similarly; while in the short-term experiments, puromycin induced less inhibition in the experimental groups than in the control group; actinomycin D inhibited the basal and ethionine groups more than the other groups; sparsomycin induced variable degrees of inhibition, with the ethionine group showing the most and the N-2-fluorenylacetamide and thioacetamide groups showing the least; hypertonic NaCl markedly inhibited all groups similarly; and CCl4 induced somewhat variable degrees of inhibition, with the thioacetamide group showing less than the other groups. In a few long-term experiments where hepatomas were evaluated in relation to surrounding liver tissue, puromycin administration induced less inhibition in the hepatomas than in the surrounding liver while actinomycin D administration induced similar inhibition in both groups. In general, in all experiments the degree of polyribosomal disaggregation was parallel to that of inhibition of protein synthesis (in vitro). The results reveal that the livers of rats fed purified diets containing selected hepatocarcinogens responsed in a variable manner in regard to protein synthesis (in vitro) and status of polyribosomal aggregation to the acute administration of selected hepatotoxic agents. (Author abstract) (23 Refs)

74. THE EFFECT OF BENZO(A)PYRENE ON DNA SYNTHESIS AND DNA POLYMERASE ACTIVITY OF RAT LIVER MITOCHONDRIA.

Salazar I, Tarrago-Litvak L, Gil L, Litvak S
Departamento de Bioquimica, Facultad de Medicina, Universidad de Chile, Carilla 6671, Santiago 7, Chile
FEBS Lett; 138(1):45-49 1982

DNA synthesis in liver mitochondria of benzo(a)pyrene (BP: 40 mg/kg)-treated rats was higher than in mitochondria from untreated rats, both at different protein concentrations and over different incubation times, but the solubilized mitochondrial DNA polymerase activity was higher in the control preparation. Dideoxythymidine triphosphate (ddTTP) inhibited DNA synthesis in whole mitochondrial preparations, with a much more profound effect in mitochondria from untreated rats. Detergent treatment showed that the difference between treated and untreated mitochondria was not due to BP effect on organelle membrane permeability. Ethidium bromide produced a polymerase inhibiting effect similar to that of ddTTP, but aphidicolin did not. (21 Refs)

75. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER FED ALPHA-NAPHTHOFLAVONE.

Li SA, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Steroid Biochem; 15:387-392 1981

Incidence of hepatocarcinogenesis was investigated in diethylstilbestrol (DES)-treated castrated and ovariectomized Syrian golden hamsters fed 0.2% alpha-naphthoflavone (ANF) in the diet. Induction of liver tumors (LT) by DES was essentially nil. When similar DES-treated castrated male hamsters were maintained on a diet containing ANF, nearly 70% developed LT. No LT were found in hamsters treated with ANF alone. Diet containing beta-naphthoflavone alone, or in the presence of DES did not induce L T. Competition with 250-fold excess nonlabeled DES for tritiated estradiol (ED) binding indicated that only the 8S moiety of estrogen receptors (ER) was specific. The specificity of ER in cytosol was indicated by minimal inhibition when either radioinert cortisol, progesterone, methyltrienolone, or triamcinolone acetonide was used at the same concentration. The binding of [3H]-ED in DES plus ANF-treated liver cytosol was saturable and of high affinity with an association constant of 0.15-1.3 x 10(9) M-1. Similar results were obtained using liver cytosol derived from untreated castrated and DES-treated hamsters. DES treatment for 3-4 mo resulted in a 2.5-fold increase in specific estrogen binding, and treatment with DES plus ANF for a similar period induced a 3.5-5-fold increase in liver ER concentration. In both treated groups when sedimented in high salt sucrose gradients, 4S nuclear binders were detected for liver ER. Cytosol-nuclear receptor translocations carried out either in the presence of nonlabeled DES or at 0-3 C exhibited little nuclear uptake of the labeled ED in all tissues examined. (37 Refs)

76. DNA METHYLASE ACTIVITY OF NORMAL LIVER, REGENERATING LIVER, AND A TRANSPLANTABLE HEPATOCELLULAR CARCINOMA.

Walker MS, Becker FF
(c/o Becker) Dept. Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Biochem Biophys; 5(3):169-173 1981

DNA methylase was obtained from regenerating rat liver (RRL) from male ACI animals in which transplantable hepatocellular carcinoma (THC 252) had been induced by exposure to N-2-acetylaminofluorene, from normal rat livers (NRL), and from THC 252 nuclei (THC). The activities of DNA methylase in crude extracts of NRL, RRL, and THC, determined by methylation of denatured Micrococcus luteus DNA, were as follows: NRL less than RRL less than THC. A similar assay with Escherichia coli and calf thymus DNAs, both single- and double-stranded, confirmed that methylase activities of the three tissues remain in the same order regardless of substrate. Methylation saturation studies performed with DNAs from the same three rat tissues showed that THC 252 DNA is hypomethylated, and that the undermethylation does not result from an inability of THC 252 methylases to methylate THC 252 DNA. The results confirm earlier findings obtained by direct analysis of 5-methylcytosine content; chromatin composition or configuration is the most likely explanation for hypomethylation. (25 Refs)

77. MEMBRANE-BOUND SIALOGLYCOPROTEINS FROM RAT LIVER AFTER COMBINED EXPOSURE TO BENZO(A)PYRENE AND SULFUR DIOXIDE.

Merkur'eva RV, Bushinskaia LI, Skvortsova NN, Dolinskaia SI, Shaternikova IS, Nozdracheva LI
Lab. Biochemistry and Hygiene of Atmospheric Pollutants, A. N. Sysin Inst. General and Community Hygiene, Moscow, USSR
Vopr Med Khim; 27(6):791-794 1981

The effect of carcinogens on metabolism of membrane-bound sialoglycoproteins (MBSGP) was studied in random-bred albino male rats. Animals were exposed to benzo(a)pyrene (BP) in combination with sulfur dioxide (SD). Within 2 wk, 6 wk, and 6 mo after exposure, rats were sacrificed and the distribution of MBSGP in the liver was determined. Combined exposure to BP and SD resulted in the increase of N-acetylneuraminic acid content in liver mitochondria and liver lysosomes, decrease of neuraminidase activity, and increase of beta-galactosidase activity. Carcinogens did not affect lipid peroxidation in the liver tissue. (20 Refs) (In RUS)

78. DECREASED ACTIVITIES OF GLYCINE AND GUANIDINOACETATE METHYLTRANSFERASES AND INCREASED LEVELS OF CREATINE IN TUMOR CELLS.

Yanokura M, Tsukada K
Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Biochem Biophys Res Commun; 104(4):1464-1469 1982

Activities of glycine methyltransferase and guanidinoacetate methyltransferase (GuM) were measured in various tissues of rats and in hepatoma of rat induced by N-2-fluorenylacetamide. Observation over a period of 8 mo showed a marked decrease of the enzymes in tumor tissue. At the same time, creatine levels in tumor increased significantly, even when GuM was not detected. (23 Refs)

79. CHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF RAT ASCITES HEPATOMA ALKALINE PHOSPHATASE: A COMPARISON WITH THE LIVER ENZYME.

Kawahara S, Ogata S, Ikehara Y
(c/o Ikehara) Dept. Biochemistry, Fukuoka Univ. Sch. Medicine, Nanakuma, Nishi-ku, Fukuoka, Fukuoka 814-01, Japan
J Biochem (Tokyo); 91(1):201-210 1982

Alkaline phosphatase was purified from plasma membrane of rat ascites hepatoma AH-130 cells by chromatographies on DEAE-cellulose and Affi-Gel Blue and preparative polyacrylamide gel electrophoresis. The yield of the purified enzyme, finally as the denatured subunits, was about three times better than that obtained previously. The purified enzyme, a glycoprotein, was analyzed for amino acid and carbohydrate compositions. The composition of the carbohydrate moiety, which amounted to about 18% by wt, indicated that both N- and O-glycosidic sugar chains were contained in the protein. The purified alkaline phosphatase (as the denatured subunits) was used to produce monospecific antibody, which was found to have the same immunological reaction with the native antigen as the antibody raised against the partially purified native enzyme. Immunological analysis by Ouchterlony double gel diffusion and quantitative immunoprecipitation demonstrated that the hepatoma enzyme was identical with that of the liver. In standard polyacrylamide gel electrophoresis at pH 8.9, the hepatoma alkaline phosphatase migrated a little more slowly than the liver enzyme. Both enzymes, however, showed identical mobility after complete removal of sialic acid from them with neuraminidase. These results suggest that the only difference between the two enzymes was in the carbohydrate moiety, especially in the sialic acid content. (Author abstract) (35 Refs)

REVIEWS AND OTHER RELATED STUDIES

80. THE NATURAL HISTORY OF NEOPLASTIC DEVELOPMENT: THE RELATION OF EXPERIMENTAL MODELS TO HUMAN CANCER.

Pitot HC
McArdle Lab. Cancer Res., Dept. Oncology and Pathology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
Cancer; 49(6):1206-1211 1982

The natural history of the development of neoplasia in experimental systems may be separated into a least three different stages, those of initiation, promotion and progression. Evidence for such distinct stages has been demonstrated in at least half a dozen different experimental systems. The stage of promotion is that stage most easily modulated. The actions of promoting agents are reversible and only effective above certain threshold levels of the promoting agent. This is in contrast to the stage of initiation, which can be induced at any dose of the carcinogenic agent in an irreversible manner. Agents exhibiting both initiating and promoting activities are termed complete carcinogens while incomplete carcinogens are those capable only of initiation. Promoting agents do not initiate but may promote cells initiated by ambient environmental means, giving the appearance of complete carcinogens in standard bioassay procedures. The stages of initiation and promotion have been extensively studied in skin and liver carcinogenesis and show almost identical characteristics. A variety of promoting agents in the human environment have been demonstrated both by experimental and epidemiologic methodologies. The importance of an understanding of tumor promotion in relation to the prevention of human cancer is emphasized. (Author abstract) (38 Refs)

81. CHEMICAL CARCINOGENESIS: A BIOLOGIC PERSPECTIVE.

Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., Room 110, Toronto, Ontario M5G 1L5, Canada
Am J Pathol; 106(2):269-296 1982

The development of cancer is discussed. Pathogenesis is related to the integration between molecular and biochemical levels of organization and cellular and tissue biologic levels. Cancer in many sites arises as a multistep process. Analysis involves study of agents and processes in carcinogenesis, initiators and initiation, promoters and promotion, subsequent sequences (progression), transfection, diet and carcinogenesis, chemotherapy and carcinogenesis, model systems for chemical carcinogenesis, and new bioassays for carcinogens and promoters. While cancer is accepted as a multistep process, models of systems available for study of genesis, properties, options, and fates of each of the sequential cell populations as steps in the development of cancer and their roles, if any, in the evolution toward cancer are not well developed. Skin and liver remain the best models for early changes. No single model exists for study of events from focal proliferation to malignant neoplasia. In almost every instance, the involved steps run together in a manner that does not permit identification and analysis of any discrete link in the chain. Despite major advances, few insights into the essential nature of carcinogen-altered cells during initiation have been generated. (167 Refs)

82. HUMAN CANCERS AND HUMAN VIRUSES.

Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

The connection between human cancers and human viruses is reviewed. Evidence of malignancies attributable to DNA viruses, similar to those of animals, is growing. A type of human leukemia retrovirus, the human T-cell leukemia virus, has been isolated. Hepatitis B virus has been shown to be of primary hepatocellular carcinoma and Epstein-Barr virus the cause of Burkitt's lymphoma and nasopharyngeal carcinoma; cytomegalovirus may be implicated in Kaposi's sarcoma and human papillomaviruses may cause skin cancer. To be implicated in oncogenesis, a virus should be found in tumor cells and be capable of transforming normal cells of the same species in vitro and inducing tumors in studies with animals. Human T-cell leukemia virus has been shown to be infectious when cultivated with human umbilical cord leukocytes, transforming them into virus-producing lines. Epstein-Barr virus causes disease only rarely on primary infection in childhood, but in adolescence or adult life it gives rise to infectious mononucleosis. Hepatitis caused by hepatitis B virus can be followed by chronic active hepatitis and cirrhosis and is a suspected cause of primary hepatocellular carcinoma. Malignant change has been reported in laryngeal papillomas, in genital warts, and in epidermodysplasia verruciformis. Factors other than viruses which influence malignant transformation are the genetic constitution and immune state of the patient. The virus-cell relation is not simple. (29 Refs)

83. 5'-NUCLEOTIDE PHOSPHODIESTERASE AND LIVER CANCER.

Tsou KC, Lo KW
Harrison/Surgical Res., Univ. Pennsylvania, Philadelphia, PA, 19104
Methods Cancer Res; 19:273-300 1982

The role of 5'-nucleotide phosphodiesterase (5'NP) in liver cancer is reviewed. Assay for 5'NP by biochemical and histochemical methods, tissue distribution of 5'NP, and methods for determination of 5'NP isozymes in human serum are described. The roles of 5'NP in liver growth and of 5'NP isozyme V (5'NP-V) in primary hepatocellular carcinoma (PHC), liver metastasis, and benign diseases are emphasized. The test for 5'NP isozyme V is a useful diagnostic aid for PHC and liver metastasis, with a very low false-negative rate. When the possibility of cirrhosis can be excluded, a consistent positive 5'NP-V for a protracted period is highly indicative of liver metastasis. The noninvasive nature and low cost of this test support its use in routine follow-up of cancer patients for liver metastasis. (144 Refs)

84. TRENDS IN CANCER RESEARCH ON CANCER FETOPROTEINS AS MARKERS.

Nishi S, Hirai H
Dept. Biochemistry, Yamanashi Medical Coll., Kofu, Japan
Nippon Rinsho; 39(10):3323-3329 1981

Discussions concerning two or three topics related to alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) chosen from cancer research studies on cancer fetoproteins used as markers, are presented. Potential for increasing the diagnostic value of serum AFP measurements was discussed. Research indicates that yolk sac tumor and hepatoma can be distinguished by analysis of serum AFP; differentiation of metastatic liver cancer and liver cancer is also thought to be possible with this method. Common bean lectin-ligated AFP, not found in benign hepatic disease, was thought to be very important for early detection of hepatic cancer and for research of precancerous conditions of hepatic cancer. The lectin-affino-electrophoresis method was thought to be an effective method for detecting differences in lectin ligands of AFP. Clinical and experimental trials of tumor radioimmunodetection with anti-CEA antibody and anti-AFP antibodies indicated that in order to maximize results, the antibody that has the highest tumor-cell blocking activity or the highest accumulating activity around the tumor cells should be used. Then, the antibody with the highest affinity for the tumor cells should be used in selecting the most appropriate antineoplastic or cytotoxic chemotherapy for the patient. (24 Refs) (In JPN)

85. CELL SURFACE GLYCOPROTEIN MARKERS FOR NEOPLASIA.

Bhavanandan VP, Davidson EA
Dept. Biological Chemistry, Milton S. Hershey Medical Center, Hershey, PA, 17033
Methods Cancer Res; 19:53-105 1982

Glycoproteins that serve as cell surface markers of neoplasia are described biochemically, in relation to viral transformation, and for various animal and human cells, and the methods employed are reviewed. The animal tumors and derived cell lines discussed include the following: neuroblastoma, melanoma, ascites, hepatoma, mammary carcinoma, lung carcinoma, and leukemias and lymphomas. Glycoprotein cell surface markers in human cells are reviewed in relation to melanoma, mammary carcinoma, lung carcinoma, colon carcinoma, ovarian carcinoma, and neuroblastoma. Metabolic labeling, isolation, purification, mapping, and structural analysis techniques applied to glycoproteins are reviewed. Future studies in this field will probably take advantage of improved methods such as isoelectric focusing gels, lectin affinity chromatography, and monoclonal antibodies. Ultimately the metabolic and genetic origin of each macromolecule must be determined. In the meantime, glycoprotein cell surface marker studies may be expected to contribute to diagnostic and immunologic approaches to management of disease. (313 Refs)

86. HEALTH HAZARDS OF PYRROLIZIDINE ALKALOIDS: A SHORT REVIEW.

Schoental R
Dept. Pathology, Royal Veterinary Coll., Royal College St., London NW1 0TU, England
Toxicol Lett; 10(4):323-326 1982

Health hazards including carcinogenicity of pyrrolizidine alkaloids (PA) are reported. PA have been correlated with veno-occlusive disease in Afghanistan and India and with liver disease in Mexican-American children. Various PA such as retrorsine, isatidine, monocrotaline, lasiocarpine, heliotrine, senkirkine, symphytine, and hydroxysenkirkine have caused tumors, neoplastic lesions, or congenital defects in rats. The incidence of primary liver cancer in Africa cannot be attributed to mycotoxins alone. Use of PA for medicinal or other purposes presents serious health hazards. (36 Refs)

87. ORAL CONTRACEPTIVES: VOLUME 5.

Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia

Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

Clinical trials, side effects, pharmacology, biochemistry, metabolism, and sociology of oral contraceptives (OC) are reviewed and discussed. Alternatives to the pill, new OC (combined oral products, OC for men), and older OC and therapeutic uses of contraceptive steroids are discussed, including their use in cancer therapy. Mortality and cardiovascular disease, hypertension, thrombosis, amenorrhea, and liver are affected by OC. Malformations and effect on offspring caused by diethylstilbestrol and other contraceptive steroids are reviewed. The role of OC in the genesis of breast, uterine endometrium, cervix, liver, and other neoplasms is discussed. OC may cause neurological, psychological, and other effects. Immunity and infection may be affected by OC. Mode of action, toxicology, contraceptive steroid metabolism, drug interactions, pharmacy, pharmacokinetics, and pharmacodynamics of OC are presented. Biochemistry and metabolism of OC are reviewed focusing on endocrinology (sex hormones, corticosteroids, protein hormones) and vitamins. (1179 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 IQE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tannenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Preda N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
In RUM

16. THE MEANING OF CANCER 'DIETS'.
Jungi WF
Abt. f. Onkologie-Hamatologie, Medizinische Klinik C, CH-9007 St. Gallen, Switzerland
MMW; 124(2):26-28 1982
In GER

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Naujoks-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Otfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Internist (Berlin); 23(1):1-9 1982
In GER

19. BLADDER CANCER.
Skrabanek P, Walsh A
Endocrine Oncology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981
In RUS

21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMCOEH, Univ Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982
In FRE

27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):455-472 1981
In RUS

29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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AUGUST, 1982

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- **EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE** **1-7**
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- **ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS** **18-30**
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. CANCER IN LIBERIA: A REVIEW OF CASES REGISTERED FROM THE LIBERIA CANCER REGISTRY 1973-1977.

Sobo AO
JFK Medical Center, P.O. Box 1973, Monrovia, Liberia
Cancer; 49(9):1945-1951 1982

Data from the Liberia Cancer Registry are reviewed for a 5-yr period. Information collected included name, age, sex, tumor site, and histologic diagnosis. Collection of accurate data was complicated by factors including inadequate diagnostic facilities, lack of documentation of patient age, and the tendency for more affluent patients to seek treatment abroad. During the first 5 yr of the registry 1,652 patients (766 men and 866 women) were registered. The total incidence of cancers was 22.5 cases/100,000 population. The incidence was fairly constant during the period, except for a decline in the last yr. Approx 10% of patients were of undetermined age. Among males the most common cancers included cancer of the liver (16.2% of cases), cancer of the prostate (11.0%), Hodgkin's disease (8.5%), Burkitt's lymphoma (8.2%), and cancer of the bladder (7.7%). Among females the most common cancers included cancer of the cervix (28.1% of cases), cancer of the breast (11.1%), cancer of the ovary (10.4%), cancer of the liver (5.4%), choriocarcinoma (4.9%), and Burkitt's lymphoma (4.2%). The frequency of lung cancer was low in both sexes, and skin cancers were less frequent than those reported in Senegal and the Cameroons. (18 Refs)

2. HEPATOCELLULAR CARCINOMA IN RURAL SOUTHERN AFRICAN BLACKS.

Kew MC, Geddes E
Dept. Medicine, Univ. Witwatersrand Medical Sch., Hospital Hill, Johannesburg 2001, South Africa
Medicine (Baltimore); 61(2):98-108 1982

The clinical presentation and natural history of hepatocellular carcinoma, as well as its association with cirrhosis and the hepatitis-B virus surface antigen, were studied in 585 Black males living in rural areas of southern Africa. In addition, the value of serum alpha-fetoprotein concentrations, serum biochemical changes, and various radiologic, isotopic and sonographic techniques in the diagnosis of hepatocellular carcinoma in this population was reviewed. The mean age of the patients was 35 yr and 40% of them were less than 30 yr of age. The most common presenting complaints were upper abdominal pain, swelling of the abdomen, wt loss and weakness. Rupture of the tumor with acute intraperitoneal hemorrhage occurred in 10% of the patients. The liver was almost always enlarged and focal tenderness was usual. An arterial bruit was heard over the liver in 23% of the patients. Ascites and splenomegaly were each present in about one-half of the patients, and 28% were jaundiced. Progressive muscle wasting was almost invariable. The tumor was rarely resectable and the patients did not respond to radiation therapy or cancer chemotherapy: the mean survival from the onset of symptoms was 11.1 wk and from the time of diagnosis 6 wk. Macronodular cirrhosis was present in the non-tumorous liver tissue at necropsy in 60% of the patients. The hepatitis-B surface antigen was detected in the serum of 62% of the patients. It was more common in younger patients, but was not related to the presence of alpha-fetoprotein. HBs antigenemia was equally common in patients with and without cirrhosis. Alpha-fetoprotein was present in high concentration in the serum of 67% of the patients and provided an excellent indicator of the diagnosis of hepatocellular carcinoma. It was more commonly found in younger patients. Biochemical changes were non-specific and did not differentiate hepatocellular carcinoma from cirrhosis or other mass lesions in the liver. Chest radiographs showed elevation of the right hemidiaphragm in 30% of the patients and multiple pulmonary metastases in 25%. One or more defects were invariably seen on isotope liver scans but the picture was not diagnostic of hepatocellular carcinoma. Blood flow scintigraphy usually showed the lesions to be vascular. Echogenic or partly echogenic and partly anechoic lesions with ill-defined edges were demonstrated on ultrasonography. Computerized axial tomograms and hepatic arteriography were useful in assessing the extent of the tumor in relation to possible resection. (Author abstract) (28 Refs)

3. PRIMARY LIVER CARCINOMA IN CHONGQING.

Liu W, Yuan A, Jin H, Hong D, Luo Y, Zhao S
Dept. Internal Medicine, Affiliated First Hosp., Chinese PLA Third Military Medical Coll., People's Republic of China
Zhonghua Neike Zazhi; 20(7):392-396 1981

Results of a mass-screening and follow-up study are described for primary liver cancer in Chongqing. A higher incidence of liver cancer was found to be associated with males 50 and 60 yr old, history of liver diseases such as hepatitis B, high levels of alpha-fetoprotein, and a positive test for hepatitis B surface antigens. Based on these findings, the importance of the follow-up of high-risk individuals and the early diagnosis of liver cancer is stressed. (3 Refs) (In CHI)

4. HEPATITIS B INFECTION AND THE PREVENTION OF PRIMARY HEPATOCELLULAR CARCINOMA: STUDIES IN SENEGAL.

Froment A, Larouze B, Feret E, Marinier E, Moustapha Sow A, London WT, Blumberg BS
(c/o Blumberg) Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Prog Med Virol; 27:133-136 1981

Continuing studies of hepatitis B (HBV) infection in Senegal include mother to child infection antigenic studies, studies of whole villages and family units within them, family studies of patients with primary hepatocellular carcinoma and families with cirrhosis or chronic active hepatitis, and studies of the interaction of protein-calorie malnutrition in children with responses to HBV. Early administration of vaccine could drastically reduce the incidence of HBV, although its effect on malnourished children is unpredictable. (11 Refs)

5. FLUORIDATION AND CANCER: AN EPIDEMIOLOGIC APPRAISAL.

Neuberger JS
Dept. Community Health, Univ. Kansas Sch. Medicine-Kansas City, Kansas City, KS
J Kans Med Soc; 83(3):134-139 1982

The relationship of water fluoridation to cancer has been studied extensively, perhaps more intensively than many other chemicals in the environment. In 1977, a paper was published under the auspices of the National Health Foundation (NHF), showing a greater increase in the cancer death rates (1940-1970) in the 10 largest American cities that began fluoridation before 1960, as compared to the 10 largest cities not fluoridated as of 1969 (excluding New York City and Detroit). The studies done by the NHF have provided the anti-fluoridationists' greatest arguments against water fluoridation. However, these studies did not meet even minimally acceptable standards for generally accepted epidemiologic research. Other studies by other scientific investigators (including several by the National Cancer Institute) indicate that fluoride is not even associated with cancer, still less a causative factor. The age-adjusted mortality rates in white Kansas residents (both sexes) for 1973-1977 were studied for cancer sites that might possibly be related to water borne carcinogens (stomach, colon, rectum, liver, pancreas, kidney, bladder, and bone), in fluoridated and nonfluoridated Kansas counties of the highest populations. (Wichita, the largest city in Kansas, is not fluoridated). The data were analyzed in terms of person-yr of exposure to fluoride. No association of artificial water fluoridation with cancer was found. It is concluded that current evidence does not support the contention that fluoride is associated with cancer. (9 Refs)

6. ENZYMES OF COLLAGEN SYNTHESIS AND TYPE III PROCOLLAGEN AMINO-PROPEPTIDE IN SERUM FROM NIGERIANS WITH HEPATOCELLULAR CARCINOMA AND OTHER MALIGNANT DISEASES.

Bolarin DM, Savolainen ER, Kivirikko KI
(c/o Kivirikko) Dept. Medical Biochemistry, Univ. Oulu, SF-90220 Oulu 22, Finland

Int J Cancer; 29(4):401-405 1982

Serum immunoreactive prolyl hydroxylase protein (S-IRPH), galactosylhydroxylysyl glucosyltransferase activity (S-GGT) and the amino-terminal propeptide of Type III procollagen [S-Pro(III)-N-P] were studied in 24 patients with primary hepatocellular carcinoma, 18 with secondary liver neoplasms and 35 with other malignant diseases but no evidence of liver involvement; this latter group included 13 patients with Burkitt's lymphoma, 11 with breast cancer and 11 with other neoplasms. Control values were determined for 60 apparently healthy Nigerians. S-IRPH and S-GGT were above the upper normal limit, defined as the mean +2 SD of the controls, in all the patients with primary hepatocellular carcinoma and all but one with secondry liver neoplasms, whereas only one S-IRPH value and three S-GGT values exceeded this limit in the patients with other malignant diseases. The mean S-Pro(III)-N-P was even more elevated than S-IRPH and S-GGT in the primary and secondary liver neoplasm cases, but was also elevated in other malignant neoplasms; about one third of the patients with no evidence of liver involvement had a concentration exceeding the upper normal limit. A high correlation was found between the values for the three assays both in primary hepatocellular carcinoma and in the whole series of malignant diseases. The data suggest that primary and secondary malignant neoplasms of the liver have a high rate of collagen synthesis. The three assays may be of some value in the diagnosis of primary hepatocellular carcinoma and secondary liver involvement in other malignant diseases, and in monitoring the treatment provided. (Author abstract) (22 Refs)

7. IS AFLATOXIN B1 A HEPATIC CARCINOGEN IN MAN?.

Franco D, Castaing D, Brechnot C, Morin J
Groupe de Recherche de Chirurgie Hepatique (INSERM U-17), Hopital Paul-Brousse, 14, avenue Paul-Vaillant-Couturier, F-94800 Villejuif, France

Gastroenterol Clin Biol; 6(2):125-128 1982

Arguments for the hepatic carcinogenicity of aflatoxin B1 (AFB) in man are discussed: AFB is a carcinogen in nonhuman primates; in vitro studies show that the metabolism of AFB by human liver microsomes is identical to that observed in rat microsomes; AFB liver toxicity in man has been well-demonstrated; epidemiologic studies have shown that hepatocellular carcinoma is particularly frequent in countries with high levels of AFB contamination of food. (32 Refs) (In FRE)

TUMOR INDUCTION IN ANIMALS

8. INDUCTION OF HEPATIC TUMORS WITH 7,12-DIMETHYLBENZ[A]ANTHRACENE IN TWO SPECIES OF VIVIPAROUS FISHES (GENUS POECILIOPSIS).

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Environ Res; 27(2):337-351 1982

Liver neoplasms were induced in two species of viviparous fishes, Poeciliopsis lucida and P monacha, by repeated short-term exposures to an aqueous suspension of 5 ppm 7,12-dimethylbenz[a]anthracene (DMBA). Predominantly hepatocellular neoplasms developed in 47 out of 106 fish surviving the period allowed for tumor development, 6-9 mo after initial exposure to DMBA. The use of short-term exposure periods of 6 hr in young fish and up to 20 hr in adults reduced stress and mortalities caused by the toxicity of DMBA at 5 ppm. A lower concentration of DMBA, 0.25 ppm, failed to induce tumors in any of the surviving 230 of 295 young fish administered repeated 20-hr exposures. This study shows for the first time that DMBA is carcinogenic to fish. (Author abstract) (8 Refs)

9. CARCINOGENICITY OF PHENACETIN: LONG-TERM FEEDING STUDY IN B6C3F1 MICE.

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Int J Cancer; 29(4):439-444 1982

Groups of 52 B6C3F1 mice of each sex were maintained on a diet containing 1.25 of 0.6% phenacetin for 96 wk and then fed a basal diet for 8 wk. Control groups consisted of 50 mice of each sex and were fed a basal diet for 104 wk. All animals were killed at the end of the experiment and all organs were examined histopathologically. Mice that died during the experiment were also autopsied and those that survived for more than 57 wk, when the first tumor was observed, were also included in the effective number of mice. Tumors were found in the kidney, liver, lung, skin, hematopoietic system (leukemia or lymphoma) and occasionally in some other organs. The dose-related induction of renal cell tumors in the male mice fed phenacetin was clearly demonstrated in this experiment. Urinary bladder lesions that developed in the mice of either sex fed 1.25% phenacetin were also considered to be due to the tumorigenicity of phenacetin. Tumors of other organs in either the phenacetin-treated or the control group were regarded as strain-related spontaneous tumors of B6C3F1 mice. (Author abstract) (20 Refs)

10. THE CHARACTERIZATION OF TRYPAN BLUE-INDUCED TUMORS IN WISTAR RATS.

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Am J Pathol; 106(3):326-331 1982

Trypan blue is an azo dye widely used for testing cell viability. The dye has been identified as a mutagen and a carcinogen. In some strains of rats, particularly Wistar rats, chronic exposure induces a reticuloendothelial neoplasm, predominantly in the liver. These tumors were studied with the use of immunologic cell membrane markers, electron microscopy, and histochemistry to characterize tumor cell type. The authors have studied this tumor in two inbred lines of Wistar rats to compare the efficacy of two previously described dye regimens on tumor incidence and to ascertain whether a short, intense exposure was as effective as chronic protracted exposure. No significant difference in tumor incidence was observed between the two regimens. These studies suggest that the tumor is composed of a macrophage-like cell that retains some characteristics of normal macrophages and that it is a reproducible model for carcinogen-induced lymphoreticular disease that may be of value in the study of some human lymphomas. (Author abstract) (22 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

11. ROLE OF ESTROGENS AS PROMOTERS OF HEPATIC NEOPLASIA.

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Dept. Pathology, Toronto Western Hosp., Toronto, Ontario, Canada
Lab Invest; 46(3):313-320 1982

The administration of estrogens to humans has been associated with the development of benign and possibly malignant hepatocellular neoplasms. This study was designed to investigate the mechanism of this association. We present a rat model that demonstrates that stilbestrol (DES) and ethinyl estradiol promote the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Eighty male and 12 female Fischer-344 rats were given a single intraperitoneal injection of either DEN (200 mg/kg of body wt) or saline. Beginning 4 wk after injection, the rats were given an estrogen or corn oil twice weekly for up to 50 wk. Treatments were stopped at the time of sacrifice or 11 to 29 wk prior to sacrifice. Estrogen treatments included high dose DES (5 mg per dose), low dose DES (0.5 mg per dose), and ethinyl estradiol (0.2 mg per dose). Male and female rats given both DEN and high dose of DES developed grossly visible hepatic hyperplasic nodules (mean, 9.1 per liver) after 20 wk of DES. Nodules also developed if the onset of DES treatment was delayed until 28 wk after initiation. Rats given DEN alone or DES alone did not develop nodules after 20 wk. Microscopic hyperplastic foci also developed in rats given DEN plus DES, DES alone, and DEN alone. The foci in rats given DES alone were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinyl estradiol was observed. Low dose DES was not effective in promoting tumor formation. The data indicate that estrogens promote hepatic neoplasia, perhaps by increasing hepatocyte mitotic activity and thereby facilitating the evolution of previously initiated cells into neoplastic clones. Comparison with human disease should be made with caution, especially because the estrogenic dose administered was approx 200-fold the usual contraceptive dose in humans. However, the analogy between this model and the development of human oral contraceptive-associated hepatic tumors is evident. It is possible that some women have latent 'initiated' cells that divide faster than the surrounding hepatocytes in response to estrogens. (Author abstract) (29 Refs)

12. SEX HORMONES AND LIVER CANCER.

Williams GM
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Lab Invest; 46(3):352-354 1982

The ability of hormones to produce tumors in endocrine-related organs of experimental animals and the phenomenon of two-stage carcinogenesis are reviewed. Liver tumor promotion, mechanisms of promotion, and the potential impact of use of estrogen-containing drugs on cancer development are discussed. The fact that human exposure to several promoters (eg phenobarbital and dichlorodiphenyl trichloroethane) does not appear to cause increased occurrence of liver neoplasms may mean that the agents were not present at high levels or for prolonged continuous exposure sufficient to impede cell-cell communication and thus promoting activity. (41 Refs)

13. CA-CALMODULIN MEDIATES THE DNA-SYNTHETIC RESPONSE OF CALCIUM-DEPRIVED LIVER CELLS TO THE TUMOR PROMOTER TPA.

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Exp Cell Res; 138(1):87-93 1982

Incubation in low (0.02 mM)-calcium medium inhibited the proliferation of T51B rat liver cells. Addition of TPA (12-O-tetradecanoyl-phorbol-13-acetate; 50 ng/ml) or calcium (1.25 mM) caused the arrested, calcium-deprived cells to initiate DNA synthesis within 2 hr and eventually to resume proliferating. The rapid DNA-synthetic response to TPA addition appeared to depend on the small amount of calcium remaining in the calcium-deficient medium, because it was blocked by correspondingly small amounts of the specific calcium chelator EGTA or La+++, which displaces calcium from the cell surface and inhibits transmembrane calcium fluxes. The common mediation of TPA and calcium actions through Ca-calmodulin complexes was indicated by the following observations: The DNA-synthetic responses to both agents were blocked by the supposedly specific Ca-calmodulin blocker trifluoperazine; the trifluoperazine-induced block was overcome by pure calmodulin; and the responses to both TPA and calcium were blocked by anti-calmodulin antibodies. (Author abstract) (35 Refs)

14. EFFECTS OF POLYCHLORINATED BIPHENYLS ON LIVER REGENERATION IN THE RAT: INFLUENCE OF POSITION AND DEGREE OF CHLORINATION.

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Arch Environ Contam Toxicol; 11(2):239-244 1982

Adult male Sprague Dawley rats underwent 70% hepatectomy and 1 day later were given an intragastric dose of polychlorinated biphenyl (PCB: 150 mg/kg/day x 6). PCBs chosen for the extent-of-chlorination (EOC) study were 4-chlorobiphenyl (4-CB), 3,4-dichlorobiphenyl (3,4-DCB), 2,4,5-trichlorobiphenyl (2,4,5-TCB), and Phenoclor (R) DP5 (DP5; commercial mixture averaging 5 chlorine atoms/molecule). PCBs chosen for the position-of-chlorine study (POC) were 4,4'-dichlorobiphenyl (4,4'-DCB), 3,3',4,4'-tetrachlorobiphenyl (3,3',4,4'-TCB), and decachlorobiphenyl (DCB). Rats were sacrificed on day 7 or 14 posthepatectomy. All livers were assayed for proteins, RNA, DNA, proteins/DNA, RNA/DNA, total lipids, phospholipids, fatty acids, cholesterol, and glycogen. Most of the parameters studied in the EOC tests rose significantly as a function of the number of chlorine atoms on the molecule. The RNA/DNA ratio increased significantly only for the DP5 group. By day 14, there were no significant differences between controls and animals treated with 4-CD, 3,4-DCB, and 2,4,5-TCB; levels of all parameters but body wt were significantly higher in rats treated with DP5 compared with controls. In the POC studies, at 14 days, animals treated with DCB and DP5 showed significant hypertrophy accompanied by hyperplasia. In animals treated with DCB, the proteins and DNA of the whole liver were significantly higher than in controls at 14 days. Thus, a close relationship was demonstrated between the structure, metabolism, excretion, and toxicity of the PCBs studied. (30 Refs)

15. PROGRESSION OF CARCINOGEN-INDUCED FOCI OF GAMMA-GLUTAMYLTRANSPEPTIDASE-POSITIVE HEPATOCYTES TO HEPATOMAS IN RATS FED A CHOLINE-DEFICIENT DIET.

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Int J Cancer; 29(4):445-450 1982

Following previous findings that feeding a choline-deficient (CD) diet to rats strongly promotes the evolution of liver cells, initiated by a chemical carcinogen, to foci of gamma-glutamyltranspeptidase (gammaGT)-positive hepatocytes, we investigated whether a CD diet could also promote the evolution of gammaGT-positive foci to hepatomas. GammaGT-positive foci were induced in male Sprague-Dawley rats by administration of a single dose of diethylnitrosamine followed by 2 wk feeding on a CD diet containing 0.02% acetylaminofluorene. Immediately thereafter, one group of rats was fed a plain CD diet and the other a choline-supplemented (CS) diet, and subgroups of animals were killed periodically for analysis of the number and size of gammaGT-positive foci and development of hepatomas. During the first 7 wk after switching the diets, the number and size of the foci increased in both groups. At 12 and 16 wk, the number and size of foci began to decline in rats fed the CS diet. However, in the CD group, there was a progressive increase in the size with coalescence of the foci, as well as development of neoplastic nodules. These lesions were followed at 20 and 28 wk by development of hepatomas at a high incidence rate. In rats fed the CS diet, a few scattered gammaGT-positive foci, and small neoplastic nodules remained in the liver at 20 and 28 wk, but no hepatomas developed. These results show that the CD diet is a potent promoter of the evolution of foci of altered hepatocytes to hepatomas, and that most of the gammaGT-positive foci are reversible lesions. (Author abstract) (37 Refs)

16. EFFECT OF DIAZEPAM ON HEPATOCARCINOGENESIS IN THE RAT.

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Dept. Pathology, Cancer Inst., Tokyo 170, Japan
Toxicol Lett; 11(1/2):155-157 1982

The tumor promoting ability of diazepam on the number and size of enzyme altered islands (EAI) in rat liver was investigated. Ten male Donryu rats were fed a diet containing 500 ppm diazepam (50 mg/kg/day) after initiation with 0.06% 3'-methyl-4-(dimethylamino)-azobenzene. Liver tissue was subsequently examined for ATPase-deficient islands (greater than 50 microns in diameter) at wk 16. Mean EAI values in the treated group were 8.64/square cm, compared to control values of 9.76/square cm. Diazepam induced neither cytomegaly nor reduction of canalicular ATPase activity in the centrolobular hepatocytes. Diazepam is apparently not a tumor promoter like phenobarbital. (14 Refs)

17. COMPARISON OF ENHANCEMENT OF GGTASE-POSITIVE FOCI AND INDUCTION OF ORNITHINE DECARBOXYLASE IN RAT LIVER BY BARBITURATES.

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Carcinogenesis; 3(2):147-150 1982

The induction of ornithine decarboxylase (ODC) by barbiturates and the ability of barbiturates to enhance neoplastic progression of chemically initiated cancer was examined in rat liver. All seven barbiturates induced ODC with barbital (7.7 fold increase) and phenobarbital (5.7 fold increase) demonstrating the most potent activity. Maximum induction of ODC by phenobarbital was obtained in 18 h. Barbital (500-5,000 ppm) and phenobarbital (500 ppm) administered in the drinking water enhanced the appearance of diethylnitrosamine (DENA)-initiated gamma-glutamyltranspeptidase (GGTase)-positive foci. Amobarbital, hexabarbital and pentobarbital did not enhance the appearance of GGTase-positive foci. In the absence of previous initiation by DENA, the enhancing regimen of the barbiturates did not cause the appearance of GGTase-positive foci. Barbiturates induced ODC activity in rat liver and enhanced the incidence of DENA initiated GGTase-positive foci. (Author abstract) (24 Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

18. METABOLIC ACTIVATION OF DIMETHYLNITROSAMINE TO MUTAGENS: ROLE OF CYTOCHROMES P-450 AND P-448.

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Toxicol Lett; 11(1/2):95-101 1982

Activation of dimethylnitrosamine (DMN) by hamster liver mixed function oxidase enzymes after pretreatment with various inducing agents was investigated. Induction of liver microsomal enzymes in male hamsters was achieved by ip administration of phenobarbitone (PBT: 80 mg/kg body wt), 3-methylcholanthrene (MCA: 20 mg/kg), or Aroclor 1254 (A-1254: 500 mg/kg) for 3 days. Ethoxyresorufin O-deethylase (EOD), NADPH-cytochrome c reductase, and cytochrome P-450 activities were assayed in liver microsomal suspension by the Ames test. Cytochrome P-450 concentrations increased to 1.29, 1.53, and 2.16 nanomole/mg protein after induction with PBT, MCA, and A-1254, respectively, compared to control levels of 0.61 nanomole/mg protein. EOD levels increased to 1.99 and 0.72 nanomole/min/mg protein after induction with MCA and A-1254, respectively, compared to control levels of 0.32 nanomole/min/mg protein. EOD levels were unaffected by PBT. NADPH-cytochrome c reductase levels increased to 63 and 80 nanomole/min/mg protein after induction with PBT and A-1254, respectively, compared to control level of 44 nanomole/min/mg protein. Cytochrome c reductase was unaffected by MCA. Pretreatment with PBT, MCA, or A-1254 did not significantly alter the capacity of liver microsomes to activate DMN to mutagens. Dimethylnitrosamine dimethylase is either not involved in the metabolic activation of DMN, or is not the rate limiting step. (21 Refs)

19. CYTOTOXICITY AND MUTAGENICITY OF DIMETHYLNITROSAMINE IN MAMMALIAN CELLS (CHO/HGPRT SYSTEM): ENHANCEMENT BY CALCIUM PHOSPHATE.

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Environ Mutagen; 4(1):7-18 1982

Conditions for use of the metabolic activator, S9, in Chinese hamster ovary (CHO) cells were studied in the hypoxanthine-guanine phosphoribosyl transferase system to quantify the mutagenicity of dimethylnitrosamine (DMN). The S9 protein was obtained from liver of Aroclor 1254-induced Sprague-Dawley rats. DMN (5 mg/ml) added to cultures of CHO cells, increased both cytotoxicity and mutagenicity with addition of S9, and each increased with increasing amounts of S9; without S9 there was no activity. A previous observation that CaCl2 led to increased cytotoxicity and mutagenicity was verified by addition to the incubation mixture of 10 milliM (mM) MgCl2, 10 mM CaCl2, or both. The greatest increase in activity was observed when both CaCl2 and MgCl2 were included. A precipitate was formed in both the S9 mix and the incubation medium at all concentrations of CaCl2, which resulted in increased activity of DMN (ie, 2.5-10 mM). Since formation of a calcium phosphate precipitate seemed the most likely explanation, the effect of added sodium phosphate was investigated. Maximum activity was obtained with addition of 50 mM sodium phosphate in addition to 10 mM CaCl2 and 10 mM MgCl2. DMN activity increased with increased amounts of S9 protein over the range 0.3-3.0 mg/ml in the S9 mix. The mutagenicity of DMN can be described as 110 mutants/10(6) cells per mM DMN per mg/ml S9 protein per hour. (20 Refs)

20. FLUORO-SUBSTITUTED N-NITROSAMINES. 2. METABOLISM OF N-NITROSODIETHYLAMINE AND OF FLUORINATED ANALOGS IN LIVER MICROSOMAL FRACTIONS.

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Carcinogenesis; 3(2):155-159 1982

In vitro metabolism of N-nitrosodiethylamine (NDEA) and of its two fluorinated analogs N-nitroso-2,2,2-trifluoroethylethylamine (NDEA-F3) and N-nitroso-bis(2,2,2-trifluoroethyl)amine (NDEA-F6) was comparatively investigated using rat liver microsomes and S-9 fraction. Aldehydes, nitrite and unchanged nitrosamines were determined. Additionally the mutagenicity was measured in a Salmonella/mammalian microsome assay. NDEA and NDEA-F3 were deethylated and, to a smaller extent, denitrosated. Dealkylation of NDEA-F3 at the fluorinated ethyl group, however, was strongly inhibited. NDEA-F6 was practically not metabolized under the in vitro conditions used. In contrast to NDEA, the mutagenicity of NDEA-F3 was at best marginal; NDEA-F6 was not mutagenic. The results show that substitution of fluorine in beta-position of NDEA strongly influences alpha-C-hydroxylation and denitrosation. (Author abstract) (20 Refs)

21. THE CHEMICAL ACTIVATION OF NON-MUTAGENIC NITRATED POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENS.

Karpinsky GE, McCoy EC, Rosenkranz HS
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Mutat Res; 92(1/2):29-37 1982

Ames assays in Salmonella strains TA1535, TA100, TA98, and nitroreductase (NRase)-deficient strains TA100NR and TA98NR were performed with 5-nitroquinoline (5-NQ), 6-nitroquinoline (6-NQ), 8-nitroquinoline (8-NQ), 1,8-dinitronaphthalene (1,8-DNN), 1-5-dinitronaphthalene, 4-nitroquinoline 1-oxide, 2-nitrofluorene, and nitrofurantoin, in the presence or absence or rat liver microsomes (S9 mix). Both 5-NQ and 6-NQ were direct-acting bacterial mutagens, but 8-NQ (a carcinogen in rats) and 1,8-DNN (an analog of 8-NQ) were not mutagenic even in the presence of S9 mix. The non-mutagenicity of 8-NQ and 1,8-DNN could be overcome chemically, in situ, by the addition of zinc (Zn) dust. Anaerobic conditions were not required for a max yield of the mutagenic product of 1,8-DNN. The mutagenicity of the 1,8-DNN product was not due to a nitro function, as shown by the fact that it was fully active even in the NRase-deficient strain TA100NR. It is concluded that although bacteria can reduce some nitrated polycyclic aromatic hydrocarbons (N-PAH) to mutagens, their NRases cannot reduce the nitro functions of all N-PAHs to the proximate mutagenic hydroxylamines. Chemical reduction of the N-PAH (ie, non-enzymatic activation) with Zn (which is compatible with the Ames bioassay) may be a useful addition to the procedure in the evaluation of the potential mutagenicity of nitro-containing chemicals. (24 Refs)

22. BENZO(A)PYRENE PHENOL PRODUCTION BY PERFUSED RAT LIVER AND ITS INHIBITION BY ETHANOL.

Reinke LA, McManus P, Kauffman FC, Thurman RG
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Cancer Res; 42(5):1681-1685 1982

A rapid and inexpensive method has been developed to estimate rates of benzo(a)pyrene phenol production by perfused rat liver. This method is based on the measurement of benzo(a)pyrene phenols utilizing a simple fluorometric procedure. Within 2 to 3 min after infusion of benzo(a)pyrene bound to serum albumin, phenols are excreted into the perfusate, primarily as glucuronide and sulfate conjugates. Maximal rates of phenol release were 8 to 10 nmol/g/hr in livers from control rats and 40 to 42 nmol/g/hr in livers from 3-methylcholanthrene-treated rats. Fasting of 3-methylcholanthrene-treated rats for 24 hr prior to perfusion experiments did not affect either the rate of phenol production or the extent of their conjugation. Ethanol (20 mM) inhibited rates of phenol formation by

50% in livers from fasted, 3-methylcholanthrene-treated rats but had no effect on benzo(a)pyrene hydroxylase activity in isolated hepatic microsomes. These data indicate that ethanol inhibits phenol formation from benzo(a)pyrene in intact liver, probably by diminishing the supply of the cofactor reduced nicotinamide adenine dinucleotide phosphate. (Author abstract) (22 Refs)

23. SELECTIVE ACTIVATION OF SOME DIHYDRODIOLS OF SEVERAL POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENIC PRODUCTS BY PROSTAGLANDIN SYNTHETASE.

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Cancer Res; 42(5):1620-1623 1982

The ability of prostaglandin synthetase (PGS) to cooxidize benzo(a)pyrene, benzo(a)anthracene, chrysene, and several of their dihydrodiol derivatives to mutagenic products was tested with salmonella typhimurium strain TA98 and TA100. The microsomal fraction of ram seminal vesicles, a known source of PGS, in the presence of the PGS substrate arachidonic acid, metabolized benzo(a)pyrene-7,8-dihydrodiol, benzo(a)anthracene-3,4-dihydrodiol, and chrysene-1,2-dihydrodiol to mutagenic products. This activity was inhibited by the PGS inhibitor indomethacin. Unlike the PGS system, however, a cytochrome P-450-reduced nicotinamide adenine dinucleotide phosphate-dependent system, present in an Aroclor 1254-induced rat liver 9,000 x g supernatant fraction, also activated the parent compounds [benzo(a)pyrene, benzo(a)anthracene, chrysene] and several other benzo(a)anthracene dihydrodiols (the 1,2-dihydrodiol, the 8,9-dihydrodiol, and the 10,11-dihydrodiol). The chrysene trans-3,4, trans-5,6, and cis-5,6 diols were not activated to mutagens by either system, Thus, the PGS system appears to be more selective than does the cytochrome P-450 system in the activation of polycyclic aromatic hydrocarbons to mutagenic products, activating only those dihydrodiols with adjacent double bonds in the bay region from which the bay-region diol-epoxides are formed. (Author abstract) (20 Refs)

24. MUTAGENICITY AND ALPHA-HYDROXYLATION OF N-NITROSOPYRROLIDINE AND N-NITROSOPIPERIDINE: A POSSIBLE CORRELATION.

Gilbert PJ, Rollmann B, Rondelet J, Mercier M, Poncelet F
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Toxicology; 22(4):345-352 1982

The rate of biotransformation of N-nitrosopyrrolidine (NPyrr) and N-nitrosopiperidine (NPip) into 1,4-butanediol (BTD) and 1,5-pentanediol (PTD), respectively, in the presence of liver post-mitochondrial fractions was investigated. Postmitochondrial fractions (S9) were obtained from homogenized rat livers and incubated with the test material. NPyrr and NPip metabolites were determined by gas chromatography. The rates of biotransformation of NPyrr and NPip were optimal after 2 hr. The quantity of BTD produced was positively correlated with the concentration of NPyrr (0-10 umole/0.1 ml) in the mixture. BTD concentrations detected in the presence of a sensitive Salmonella strain was lower, but still positively correlated with NPyrr concentration. Both mutagenicity and metabolism of NPYrr were related to the concentration of S9 liver fractions and required the presence of disodium salt (NADP). With NPip a similar correlation was observed between the mutagenic activity and dose of PTD undetected in the presence of sensitive Salmonella. The metabolic mechanism for NPyrr and NPip is apparently an NADPH-dependent alpha-hydroxylation by which the cyclic nitrosamines were converted into mutagenic intermediates. (12 Refs)

25. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

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Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK+/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (2.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

26. DISTRIBUTION AND RETENTION OF BENZO(A)PYRENE IN RATS AFTER INHALATION.

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Toxicol Lett; 11(1/2):35-42 1982

The distribution and retention of inhaled radioactive benzo(a)pyrene (BA) was determined in rats. Twenty-four male Fischer-344 rats were exposed for 1 hr to BAP (500 ug/liter air). Tissue, urine, and fecal radioactivity analyses were performed 0, 3, 6, 12, 24, or 48 hr after exposure. Significant amounts of BAP were found in the stomach, small intestine, trachea, lungs, nasal turbinates, larynx, tracheobronchial lymph nodes, kidneys, and liver immediately after exposure. Fifty per cent of the radioactivity cleared from the respiratory tract within 2-3 hr; the remaining cleared between 25 and 56 hr. Fifty per cent clearance of BAP from the liver was obtained in 6 hr. BAP and metabolite concentration in the kidney reached a max value 6 hr after exposure; subsequent clearance was at a constant rate. Radioactivity levels in the spleen, brain, and testes were lower than other major organs, and remained constant for 24 hr after exposure. Radioactivity accumulated rapidly in the cecum and large intestines and subsequently decreased at a constant rate. Excretion of radioactivity was primarily via the feces. Additional studies are necessary to determine the potential mutagenic or carcinogenic risk of BAP exposure in some tissues. (16 Refs)

27. SIMILAR LEVEL OF METABOLIC ACTIVATION OF BENZO(A)PYRENE IN PERFUSED RAT LUNG AND LIVER AND PROTECTION OF LUNG BY LIVER IN A COMBINED PERFUSION SYSTEM.

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(c/o Kahl, G.) Dept. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, D-6500, Mainz, Germany
Biochem Biophys Res Commun; 105(2):596-602 1982

The binding of benzo(a)pyrene metabolites to DNA, RNA, and protein in perfused rat liver and lung in situ and the influence of the liver on the level of nucleic acid and protein modification by benzo(a)pyrene in the lung were investigated. In the liver of 5,6-benzoflavone pretreated rats, irreversible binding of metabolically activated benzo(a)pyrene to both nucleic acids and protein reaches a peak at 15 min and then declines. In contrast, binding in the lung continuously increases over the 2 hr perfusion period. The extent of binding is of the same order of magnitude in the liver and lung of cytochrome P-448-induced (ie 5,6-benzoflavone-induced) animals. At 15 min, binding to both DNA and RNA in the liver exceeds binding to nucleic acids of the lung by a factor of 3-6; this relations is nearly reversed after 2 hr of perfusion. Protein binding is more pronounced in the lung than in the liver over the entire 2 hr perfusion. The longer persistance of benzo(a)pyrene binding in the lung may contribute to the fact that the lung and not the liver is the target organ of benzo(a)pyrene carcinogenesis. Following the insertion of a liver into the perfusion circuit of the lung, the total irreversible binding of metabolically activated benzo(a)pyrene to DNA, RNA, and protein is reduced, this effect being more pronounced in 5,6-benzoflavone-induced animals. Thus the high detoxication capacity of the liver can protect other organs having lower xenobiotic metabolizing activity against benzo(a)pyrene. (16 Refs)

28. METABOLISM OF 3-HYDROXYBENZO(A)PYRENE IN RAT, ISOLATED HEPATOCYTES AND KIDNEY.

Yamazaki H, Kagita T, Fujiwara M, Kishi T, Kakiuchi Y, Watabe K, Kondo M
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Chemosphere; 11(3):349-353 1982

Adult male Sprague-Dawley rats were given an iv dose of tritiated (0.1 uCi) 3-hydroxybenzo(a)pyrene (3-OHBaP). Urine was collected at hr 24 and 48. The same amount of tritiated 3-OHBaP was also incubated with perfused rat hepatocytes and with sliced rat kidney at 37 C for 2 or 3 hr; extracts were obtained at hr 0.5, 1, 2, and 3 (kidney only). At hr 24 the urine contained benzo(a)pyrene-9,10-diol, benzo(a)pyrene-4,5-diol, benzo(a)pyrene-1,6-quinone, and 3-OHBaP. At hr 48 the urine still contained all of them, but the 9,10-diol was now present only as a glucuronide compared to none at hr 24. All of these metabolites and 3-OHBaP were found in the hepatocytes at all times except for no 1,6-quinone at hr 1, mainly as quinones at all times and 9,10-diol at hr 2. The 3-OHBaP was assayed only as a glucuronide; the 9,10-diol was never found as a glucuronide. In the kidney extracts only quinone metabolites were identifiable at hr 0.5 and 1. At hr 2 all the diols were present too, mainly 4,5-and 7,8-. At hr 3 not much change had occurred, but the 9,10-diol was present also as a glucuronide; 3-OHBaP was present as a glucuronide. (9 Refs)

29. IDENTIFICATION OF METABOLITES OF BENZO[B]FLUORANTHENE.

Amin S, LaVoie EJ, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 3(2):171-174 1982

The metabolism by rat liver 9,000 x g supernatant of the environmental carcinogen benzo[b]fluoranthene was investigated. The major metabolites were identified, by comparison to synthetic samples, as 5-and 6-hydroxybenzo[b]fluoranthene and 4- or 7-hydroxybenzo[b]fluoranthene. The principal dihydrodiol metabolite formed under these conditions was trans-11,12-dihydro-11,12 dihydroxybenzo[b]fluoranthene, which was identified by comparison to the synthetic compound. 1,2-Dihydro-1,2-dihydroxybenzo[b]fluoranthene was identified, by its mass spectrum and by comparison of its uv spectrum to that of a synthetic model compound, 11-ethylidene-11H-benzo[b]fluorene. No evidence was obtained for the formation of 7b,8-dihydro-7b,8-dihydroxybenzo[b]fluoranthene or trans-9,10-dihydro-9,10-dihydroxybenzo[b]fluoranthene. The latter would be the precursor to a bay region dihydrodiol epoxide of benzo[b]fluoranthene. (Author abstract) (24 Refs)

30. THE INFLUENCE OF VARIOUS ENZYME INDUCERS ON THE MICROSOMAL METABOLISM OF 7,8-BENZOFLAVONE.

Coombs MM
Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Carcinogenesis; 3(2):229-230 1982

Comparative in vitro metabolic experiments with 7,8-benzoflavone using microsomes prepared from the livers of control Sprague-Dawley rats or from rats of the same strain treated with phenobarbitone, 3-methylcholanthrene, or Aroclor 1254 (known inducers of hepatic cytochrome P450 mixed function oxidases) disclosed variable amounts of the three metabolites previously reported, namely the 5,6-epoxide, 9,10-dihydro-9,10-diol, and the 5 (or 6)-phenol. Microsomes from phenobarbitone-treated rats gave in addition a small amount of the 5,6-dihydro-5,6-diol, identified by mass spectrometry and uv spectroscopy. The apparent discrepancy between our previous results and those of Nesnow and Bergman is therefore partly resolved, although the absence of the 9,10-diol from their products remains unexplained, but may have resulted from their use of rats of a different strain. (Author abstract) (4 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

31. THE LIPID NATURE OF A TUMOUR-ASSOCIATED AUTOANTIGEN FROM A CHEMICALLY INDUCED RAT HEPATOMA.

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Dept. Immunology, Univ. Stockholm, S-106 91 Stockholm, Sweden
Scand J Immunol; 15(2):187-193 1982

The target antigens from the complement-dependent cytotoxic antibodies in D23 tumor-bearer serum (TBS) from rats carrying the chemically induced D23 hepatoma were extractable from extranuclear membranes of tumors with chloroform/methanol. The antigenic activity, measured by inhibition of

D23 TBS cytotoxicity against D23 cells, was recovered in the phospholipid-containing fraction after silica gel chromatography. Preparative thin-layer chromatography (in chloroform/methanol/0.25% CaCl2) revealed that the antigenic activity migrated similarly to phosphatidylethanolamine and cardiolipin, although these phospholipids did not cause the inhibition seen with the antigenic fractions. Phospholipase A2 digestion of the phospholipid fraction did not affect the antigenic activity nor did it alter the mobility of the antigen when analyzed with thin-layer chromatography. From these results it was concluded that the antigen extracted from D23 hepatoma may be of phospholipid nature, although its molecular identity remains to be established. (Author abstract) (25 Refs)

32. ALPHA1-FETOPROTEIN AND TENNESSEE ANTIGEN IN HEPATOCELLULAR CARCINOMAS AND IN METASTATIC LIVER CANCER.

Polterauer P, Muller M
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Wien Klin Wochenschr; 94(4):102-105 1982

Alpha-1-fetoprotein (AFP) and Tennessee antigen (TA) were evaluated in sera of 23 patients (15 men, 8 women; 24-78 yr old) with histologically confirmed hepatic carcinoma [15 had malignant hepatomas (MH) in liver free of cirrhosis, 3 had MH associated with alcoholism, 2 had MH after hepatitis, 1 each had MH associated with hemochromatic liver, cryptogenic liver cirrhosis, and chronic aggressive hepatitis], and 20 patients (10 men, 10 women; 35-78 yr old) with histologically confirmed hepatic metastases (HM) from primary cancers (12 colorectal, 2 gastric, 2 salivary gland, 1 each pulmonary, mammary, bladder, and thyroid). Radioimmunoassay was used for determination of AFP with normal values up to 9 nanog (ng)/ml, suspicious for MH greater than 174 ng/ml, and diagnostic for MH greater than 6074 ng/ml. Inhibition of hemoagglutination was used for measuring the TA with normal values up to 7.7 units/ml. AFT values were elevated in 87% of the patients with MH and 65% had values that were suspicious for MH. TA values were elevated in 87% of the patients with MH, but the TA values were in normal range in 85% of the patients with HM. (7 Refs) (In GER)

33. HEPATITIS B ANTIGEN IN SERUM OF THE PATIENTS WITH CHRONIC LIVER DISEASES AND MALIGNANT HEPATOMA.

Libman E, Stojsic S, Marton B, Lemberger J
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Med Pregl; 34(9/10):389-392 1981

Serum radioimmunoassay (RIA) was used for the determination of hepatitis B surface antigen (HBsAg). Serum of 30 healthy controls (HC), of 50 blood donors (BD: 20-54 yr old), of 96 patients with chronic persistent hepatitis (CPH), of 8 with aggressive hepatitis (AH), of 95 with alcoholic hepatic cirrhosis (AHC), of 10 with postnecrotic hepatic cirrhosis (PHC), and of 20 with malignant hepatoma (MH) was analyzed for HBsAg. RIA was also used for the determination of alphafetoprotein (AFP). Increased values of HBsAg were observed in 6 of the BD, in 22 of the patients with CPH, in 5 with AH, in 4 with AHC, in 3 with PHC, and in 1 with MH. Increased values of AFP were found in 2 patients with AH, in 6 with AHC, in 6 with PHC, and in 14 with MH. Concentrations of AFP were 18-11,812 nanog/ml in patients with MH. One patient with primary MH and increased value of HBsAg, did not have increased value of AFP. (28 Refs) (In SCR)

34. IMMUNOHISTOCHEMICAL STUDIES ON THE ASSOCIATION BETWEEN HEPATITIS B SURFACE ANTIGEN AND PRIMARY HEPATOCELLULAR CARCINOMA WAS EVALUATED IN BIOPSY AND AUTOPSY MATERIAL.

Volc-Platzer B, Hanak H, Weiss W, Denk H
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Wien Klin Wochenschr; 94(4):108-114 1982

Relationship between hepatitis B surface antigen (HBsAG) and primary hepatic carcinoma (PHC) was evaluated in 15 biopsies of patients with PHC [10 associated with hepatic cirrhosis (HC)]; in 107 autopsies of patients with PHC (102 associated HC); and in 90 patients with HC without PHC. HBsAG was determined using the peroxidase-antiperoxidase method. Among 15 biopsies, 5 showed only PHC tissue, and 10 showed PHC and normal tissue; HBsAG was found only in normal tissue of 2/10 biopsies. (66 Refs) (In GER)

35. FELINE LEUKEMIA VIRUS AND HEPATITIS B VIRUS: A COMPARISON OF LATE MANIFESTATIONS.

Francis DP, Essex M, Maynard JE
Hepatitis Lab., Bureau Epidemiology, Center for Disease Control, 4402 North 7th St., Phoenix, AZ, 85014
Prog Med Virol; 27:127-132 1981

Similarities and differences between feline leukemia virus (FeLV) and hepatitis B virus (HBV) are reviewed, and estimates of outcomes of HBV infection are made in a manner similar to that used with FeLV from infection-rate and mortality statistics. Cancer is probably a rare manifestation of HBV infection in the United States (0.4% of infections), whereas deaths from cirrhosis are a much more common outcome (1.8%). HBV fits a pattern expected for a naturally-occurring oncogenic virus, and treatment and research should be geared to such a hypothesis. (15 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

36. CYTOCHEMICAL CHARACTERISTICS OF ISOLATED RAT HEPATOCYTES DURING DIETHYLNITROSAMINE CARCINOGENESIS.

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R. E. Kavetskij Inst. Problems of Oncology, Kiev, USSR
Eksp Onkol; 4(1):55-60 1982

Morphological and histochemical changes in the liver during hepatocarcinogenesis were studied in random-bred albino rats subjected to a daily po administration of 0.02% diethylnitrosamine (DENA). Rats received carcinogen for 15 wk. Within different time periods after the initiation of DENA administration, animals were sacrificed, and the isolated hepatocytes were subjected to cytochemical examination. DENA administration resulted in progressive increase of cell polymorphism and cytochemical heterogeneity of hepatocytes. Significant increase of the number of large hepatocytes with large cell nucleus was observed 1 mo after the initiation of DENA administration. Excessive glycogen accumulation and decrease of ATPase activity were first detected 3 wk after the onset of DENA administration. Exposure to DENA did not produce any significant changes in activities of glucose-6-phosphatase, acid phosphatase, acid DNAse, or nonspecific esterase. (32 Refs) (In RUS)

37. PALE EOSINOPHILIC INCLUSIONS SIMULATING GROUND-GLASS APPEARANCE OF CELLS OF HEPATOCELLULAR CARCINOMA.

Nakanuma Y, Kono N, Ohta G, Shirasaki S, Takeshita H, Watanabe K, Tsuda S, Yoshizawa H
Second Dept. Pathology Sch. Medicine, Kanazawa Univ., Takaramachi 13-1, Kanazawa 920, Japan
Acta Pathol Jpn; 32(1):71-81 1982

Pale eosinophilic inclusions simulating ground-glass appearance were observed in cells of hepatocellular carcinoma. They were round or elliptical in shape, and their size was about 14 um in diameter. Light eosinophilia and fine granulation with homogeneous appearance were delineated from other cellular materials. They were negative for HBsAg, blood plasma proteins including alpha1-antitrypsin, and alpha-fetoprotein by immunohistochemical stainings. Ultrastructurally, they were well-demarcated and consisted of homogeneous finely granular matrix. Histological, histochemical and ultrastructural features were different from several intracellular inclusions hitherto reported on hepatocellular carcinoma. These changes may represent a deposition of secretory proteinous materials in cells of hepatocellular carcinoma, but their chemical and antigenetical content could not be identified. (Author abstract) (25 Refs)

38. HIGHLY PERMEABLE CONTACTS AND ELECTRICAL CHARACTERISTICS OF NORMAL LIVER TISSUE. II. STRUCTURAL MODEL AND ESTIMATION OF INDUCED MOUSE HEPATOMA CELL MEMBRANE PERMEABILITY.

Sharovskaia IuIu, Mittel'man LA, Smolianinov VV, Chailakhian LM
Interdisciplinary Res. Lab. Molecular Biology and Biological Chemistry, Moscow Univ., Moscow, USSR
Tsitologiia; 24(1):26-34 1982

The values of specific resistances of nonjunctional (Rm) and junctional (Rj) membranes of induced murine hepatoma cells were calculated by means of the syncytium theory equations and on the basis of input resistances and electronic potential spread curves. For the three-dimensional model with three contacts per cell, Rm and Rj were found to be 3,300-5,600 Ohm x square centimeter (cm2) and 2 x 10(-2) Ohm x cm2, respectively. The corresponding values for normal liver cells were 2,400-7,200 Ohm x cm2 and 6.5 x 10(-2) Ohm x cm2. (5 Refs) (In RUS)

39. CYTOPATHOLOGY OF PRECURSOR LESIONS OF INVASIVE CARCINOMA OF THE GALLBLADDER. A STUDY OF BILE ASPIRATED FROM SURGICALLY EXCISED GALLBLADDERS.

Alonso de Ruiz P, Albores-Saavedra J, Henson DE, Monroy MN
Departamento de Patologia, Facultad de Medicina, Universidad Nacional Autonoma de Mexico, Apartado Postal 7-1023, Mexico, 7, Mexico
Acta Cytol (Baltimore); 26(2):144-152 1982

Bile aspirated from 374 gallbladders immediately after they were excised with cholelithiasis or cholecystitis was examined cytologically. Smears from 250 cases were considered adequate for cytologic analysis, and the findings were correlated with the histologic diagnosis. Poor correlation was obtained with hyperplasia (28%) and dysplasia (25%). In contrast, cytohistologic correlation was good for cases of carcinoma in situ (4 of 6 cases) and invasive carcinoma (7 of 7 cases). Several reasons are given for the discordance between cytologic and histologic diagnoses of hyperplasia and dysplasia. The experience gained in this study may serve in the preoperative identification of these cancer precursors in high-risk patients. (Author abstract) (13 Refs)

40. LONG-TERM FATE OF THE BILE DUCT CELLS PROLIFERATED DURING CHRONIC THIOACETAMIDE POISONING.

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Int J Tissue React; 4(1):55-61 1982

The proliferation of the bile duct cells of Sprague-Dawley rats, induced by a continuous feeding of thioacetamide (TAA: 0.05% solution in drinking water over a 4-mo period) was investigated. At the end of the exposure period, the liver was cirrhotic, with many bile duct proliferations surrounded by a small amount of connective tissues. Three types of cells were observed in the newly-formed ducts: bile duct cells similar in histochemistry to controls; highly specialized cells suggesting intestinal metaplasia; and poorly differentiated oval cells. All the neoformed bile duct cells stained positively for gammaglutamyltranspeptidase (GGT) and negatively for butyrocholinesterase (BCE). By 1-2 mo after TAA withdrawal, most of the biliary proliferations disappeared. In those remaining, while the oval cells disappeared completely, the number of highly specialized cells had increased. The bile duct cells retained the same histochemical appearance, although some cells were now BCE positive. Five to 8 mo after TAA withdrawal, some large areas of cholangiofibrosis persisted within normal-looking tissue and the bile duct proliferations were surrounded by a remarkable amount of connective tissue. Most of the cells were PAS positive. The number of cells showing GGT activity decreased while the number staining for BCE increased. It is proposed that the normal-looking bile duct cells seen at the end of the TAA poisoning, but which slowly disappear during withdrawal, represent a reactive hyperplasia but have no role in the carcinogenetic process. The PAS positive cells, which remain during the recovery period within some cholangiofibrotic areas and exhibit strong BCE activity (characteristic of cholangiocarcinomas) may be considered preneoplastic. (15 Refs)

41. ULTRASTRUCTURAL CHANGES IN LIVERS OF YOUNG AND AGING RATS EXPOSED TO METHYLATED BENZENES.

Bowers DE, Cannon MS, Jones DH
Sch. Dental Medicine, Southern Illinois Univ., Alton, IL, 62002
Am J Vet Res; 43(4):679-683 1982

Ultrastructural examination was conducted on livers of young rats which were given (intraperitoneal injection) several methylated benzenes (73 mg/kg of body weight) for 3 consecutive days and on livers of aging rats (12 to 19 months old) which were fed methylated benzenes in the diet (200 mg/1,000 g of feed) for periods of 1, 2, 3, and 6 months. The young animals demonstrated white, raised, nodular lesions along the free margins of the liver. The lesions in young animals consisted of lipid droplets surrounded by macrophages and fibroblasts. Some fibroblasts in these lesions appeared to be active in collagen synthesis. Mast cells and eosinophils also occurred in the lesions. Hepatocytes in these young animals appeared morphologically normal. In contrast, hepatocytes in the aging rats developed 2 types of vacuoles. The 1st type of vacuole was bound by a double-unit membrane - the outer unit membrane possibly derived from smooth endoplasmic reticulum; it contained a mottled, globular, electron-lucent material. The 2nd type of vacuole was peripherally located in hepatocytes, was single membrane-bound, and occasionally was observed opening into the space of Disse (spatium perisinusoideum). Our observations indicated that acute exposure (3 days) to at least some methylated benzenes does not cause ultrastructurally observable abnormalities in hepatocytes of young rats, but chronic oral ingestion of some can cause formation of vacuolar structures in aging rat hepatocytes. (Author abstract) (16 Refs)

42. THE HISTOCHEMICAL DEMONSTRATION OF GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY IN DIFFERENT POPULATIONS OF RAT LIVER CELLS DURING AZO DYE CARCINOGENESIS.

Daoust R
Institut du Cancer de Montreal, Hopital Notre-Dame, Montreal, Quebec, Canada
J Histochem Cytochem; 30(4):312-316 1982

To better assess the reliability of gamma-glutamyl transpeptidase (gamma-GTase) as a marker of preneoplastic liver lesions and hepatomas, the gamma-GTase activity of different cell populations was examined in liver sections from rats fed 4-dimethylaminoazobenzene. The results indicated that the biliary ductular cells in trabeculae of cirrhotic livers may exhibit appreciable gamma-GTase activity in addition to that shown by islands of regenerating parenchyma. At later stages of azo dye carcinogenesis, the epithelial cells of bile duct cysts and cholangiomas, as well as those of hepatomas, gave positive reactions for gamma-GTase. Thus biochemical data on liver gamma-GTase in different models of hepatocarcinogenesis cannot be translated directly in terms of alterations in a particular cell type unless such interpretation is justified by parallel histochemical investigations. (Author abstract) (63 Refs)

43. BIOCHEMICAL AND MORPHOLOGICAL CHARACTERIZATION OF GLYCOGEN-STORING EPITHELIAL LIVER CELL LINES.

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Div. Cytopathology. Inst. Experimental Pathology, German Cancer Res. Center, D-6900 Heidelberg, W. Germany
Exp Cell Res; 138(1):1-14 1982

Three cell lines (c1I, c1II and c2I) were cloned from a primary culture of hepatocytes; two of them store glycogen in excess (c1I and c1II), the third clone (c2I) shows low glycogen content. Several morphological and biochemical criteria indicate an epithelial, most probably hepatocellular origin of the cell lines; the glycogen areas in c2I are composed of alpha-particles, whereas the large glycogen deposits in c1I and c1II are formed by beta-particles. After prolonged culturing c2I also begins to store beta-particulate glycogen. The cell lines form desmosome-like junctions and contain intermediate-sized filaments of the cytokeratin type which have so far been found exclusively in epithelial cells. All cells have low glucose-6-phosphatase activity which is ultrastructurally restricted to the membranes of the smooth and rough endoplasmic reticulum including the nuclear envelope. The cell lines reveal high activity of glucose-6-phosphate dehydrogenase. The high glycogen content of the cells does not change during the course of one passage. In the glycogen-storing cells glycogen phosphorylase increased slightly or remains constant during one passage, whereas synthetase decreases significantly. The remarkable parallel between the properties of the glycogenotic cell lines and preneoplastic glycogen storage foci of the liver of carcinogen-treated rats is discussed. (Author abstract) (52 Refs)

44. DIFFERENTIAL PERSISTENCE OF CHROMOSOMAL DAMAGE INDUCED IN RESTING RAT-LIVER CELLS BY X-RAYS AND 4.2-MEV NEUTRONS.

Tates AD, Broerse JJ, Neuteboom I, De Vogel N
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Mutat Res; 92(1/2):275-290 1982

Young male Wistar rats (35-45 days old) or mature WAG/Rij female rats (24 wk old) were exposed to total-body irradiation with x-rays (XR: 100-400 rads) or 4.2 million electron volt neutrons (NR: 25-100 rads). Partial hepatectomy was performed 1 day-3 mo after irradiation; 2-3 days postoperatively, the remaining liver was perfused and isolated hepatocytes were examined for cytoplasmic micronuclei. Both XR and NR caused a dose-related increase in the occurrence of micronuclei. The plateau of the dose-effect curve was observed at 400 rads XR and 50 rads NR. In the XR group, the frequency of micronucleated hepatocytes decreased with increasing time intervals after irradiation; the frequency at 3 mo was not significantly different from the control value. In the NR group, the frequencies of micronucleated hepatocytes remained constant at all time intervals studied. The progressive decline in the frequencies of hepatocytic micronuclei after XR exposure may be explained by two mechanisms operating simultaneously: slow, long-term repair of chromosomal damage and mitotic selection against cells bearing substantial amounts of chromosomal damage. The mechanisms did not seem to be in effect in the NR group. The relative biologic effectiveness of NR in the ascending portion of its dose-effect curve was about 4 relative to XR. The long-term effects of XR and NR should be compared at lower doses, at which cell regeneration induced by XR is not demonstrable. Such experiments might provide more information on possible long-term repair processes in resting (GO) liver cells with XR-induced chromosomal damage. (26 Refs)

45. STUDIES ON DNA CONTENT OF HEPATOCYTES IN CIRRHOSIS AND HEPATOMA BY MEANS OF MICROSPECTROPHOTOMETRY AND RADIOAUTOGRAPHY.

Koike Y, Suzuki Y, Nagata A, Furuta S, Nagata T
Dept. Internal Medicine, Shinshu Univ. Sch. Medicine, Matsumoto 390, Japan
Histochemistry; 73(4):549-562 1982

Ploidy patterns of DNA content of hepatic cell nuclei of patients with various liver diseases were studied with Fuelgen-cytofluorometry (33 patients) and tritiated thymidine radioautography (36 patients). Microspectrophotometry demonstrated wide variations in the distribution of ploidy patterns, from hypodiploid to hyperpolyploid in the noncancerous parts of a cirrhotic liver containing hepatoma. In normal liver, most of the binucleate cells were diploid. In sublobular liver cirrhosis, approx 90% of the mononucleate cells were hypodiploid and diploid. In multilobular liver cirrhosis, most of the mono- and binucleate cells were diploid; the appearance of polyploid cells was 38.23 +-5.65% of hepatocytes. In multilobular liver cirrhosis with a high labeling index in a patient who subsequently developed hepatoma, mono- and binucleate cells contained significant amounts of hypodiploid, diploid, hyperdiploid, triploid, hypotetraploid or tetraploid nuclei. In noncancerous parts of hepatoma with cirrhosis, the mononucleate cells exhibited a decrease in diploid and an increase in hyper- to tetraploid nuclei, while binucleate cells exhibited diploid-tetraploid nuclei; the appearance rate of polyploid nuclei was 54.45 +-7.2%. In differentiated hepatoma cells, diploid cells were more common than in undifferentiated cells; the appearance rate of polyploid cells was 79.74 +-17.08%. Radioautography demonstrated a mean labeling index of 0.43 +-0.08% in normal liver and most other liver diseases; that for noncancerous parts of hepatoma with cirrhosis was as high as 5.98 +-1.73%. The possibility that hepatocytes in noncancerous parts of hepatoma have deranged cell-kinetics which might be a driving factor for the development of malignancy. (28 Refs)

46. NATURALLY OCCURRING POLYPOID HYPERPLASIA AND PAPILLOMA IN GALLBLADDERS OF THE FAT SAND RAT (PSAMMOMYS OBESUS TERRAESANCTAE THOMAS).

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Vet Pathol; 19(3):230-238 1982

The gallbladders of 256 fat sand rats (131 males and 125 females) 7 to 41 mo old were studied histologically. None of the sand rats had been used in experimental procedures prior to death. Diffuse polypoid hyperplasia or papilloma of the gallbladder mucosa was found in 49 sand rats. Of these lesions, 45 were present in 126 sand rats in the second half of their lifespan. Neither concretions nor signs of chronic inflammation were seen. Signs of focal epithelial growth activity were seen in either form of lesion. Epithelial hyperplasia was excessive in two gallbladders, and one was diagnosed as carcinoma-in-situ. The papilloma in one sand rat revealed transition to adenocarcinoma, with penetration into the deep layers of the gallbladder. Preneoplastic nodules were found in the liver as frequently as reported previously, but they were related to gallbladder lesions. The unusual high incidence of spontaneous epithelial proliferation in the gallbladder mucosa in sand rats of both sexes through several generations suggests this strain as a model in the experimental study of tumorigenesis in the gallbladder. (Author abstract) (24 Refs)

47. THE PATHOLOGY OF LIVER TUMOURS IN THE DOG.

Trigo FJ, Thompson H, Breeze RG, Nash AS
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J Comp Pathol; 92(1):21-39 1982

A clinicopathological study of 49 primary and 129 secondary liver tumors from 1,867 canine necropsies is reported. Of 49 cases of primary liver neoplasia, 8 were hepatocellular adenomas, 6 cholangiocellular adenomas, 18 hepatocellular carcinomas, 13 cholangiocellular carcinomas, 1 a combined hepatocholangiocellular carcinoma, 2 hemangiosarcomas, and 1 fibrosarcoma. Of the 129 secondary liver tumors, 67 were lymphosarcomas, 15 splenic hemangiosarcomas, 9 pancreatic carcinomas, and 38 were other types of tumors. Benign tumors were less common than malignant tumors, and were generally of no clinical significance. A prevalence of 1.71% malignant epithelial tumors was higher than previous reports for dogs. Hepatocellular carcinoma (HCC) was approx equally prevalent with cholangiocarcinomas (CAC). Loss of wt and dullness were more severe and common in CAC than in HCC, while enlargement of the abdomen and palpation of an abdominal mass were more common with HCC. The gross appearance at autopsy of HCC and CAC was not sufficiently different to allow a diagnosis. In general, tumors derived from liver cells were massive, lobulated, soft, and yellowish-brown while those from bile duct epithelium were nodular, umbilicated, firm and greyish-white. Jaundice was observed in only 9/97 cases with metastatic tumors and in three of these, obstruction of the common bile duct was the cause. In a dog with a tumor, the combination of hepatomegaly and elevation in the activities of alkaline phosphatase, SGOT, and SGPT may indicate metastases to the liver. Some of these findings were compared with those reported for liver tumors in man. (28 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

48. EARLY CHANGES IN MITOCHONDRIAL MONOAMINE OXIDASE ACTIVITY OF RAT LIVER DURING HEPATOCARCINOGENS FEEDING.

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Excerpta Med Int Congr Ser; 564():241-250 1982

The effects of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), 2-acetylamino-fluorene (2-AAF), 2-aminofluorene (2-AF), 2-nitrofluorene (2-NF), and N-hydroxy-2-AAF on mitochondrial monoamine oxidase (MAO) activity of rat liver are reported. Male and female Donry rats were used. Significant decrease (70%) in MAO-B activity was observed during 3'-Me-DAB feeding. The changed patterns of MAO-B activity are similar to those of rat hepatoma. When rats were fed a diet containing 0.05% 2-AAF, a remarkable decrease of MAO-B activity was observed, while MAO-A activity was not affected. In female rats fed 0.05% 2-AAF diet, MAO-B activity was not changed after 1 wk, but decreased to some extent at 3 and 12 wk after the exposure to the carcinogen. The intensity of the MAO-B activity decrease in female rats was to a lesser extent as compared to that of male rats at each time period. 2-AAF higher concentrations inhibited MAO-B activity when added in vitro, but MAO-A activity was strongly inhibited by addition of 10(-7) M 2-AAF. Each compound of fluorene derivatives tested was administered po at a dose of 200 micro moles/kg daily for 7 days. N-hydroxy-2-AAF and 2-AF decreased MAO-B activity. 2-NF did not show any effect under experimental conditions. Effect of 2-AAF on MAO-B activity was examined in thyroxine-treated and riboflavin-deficient rats. An additive decrease of MAO-B activity was observed in 2-AAF and thyroxine-treated animals as compared to the decrease produced by the separate administration. When rats were fed riboflavin-deficient diet for 2 wk, MAO-B activity was decreased to 60% of the control levels. The decreased activity tended to return to control levels if rats were fed the basal diet again. (27 Refs)

49. INFLUENCE OF AGE, SEX AND CANCER ON THE ACTIVITIES OF GAMMA-GLUTAMYL TRANSPEPTIDASE AND OF DIPEPTIDYL AMINOPEPTIDASE IV IN RAT TISSUES.

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Faculty Pharmaceutical Sciences, Nagasaki Univ., Bunkyo-machi 1-14, Nagasaki 852, Japan
Enzyme; 27(2):114-118 1982

Gamma-glutamyl transpeptidase (GTP; EC 2.3.2.2) is an enzyme known to show activity changes during development and carcinogenesis. Its activity was measured in the livers and lungs of female and male rats of different ages, in Morris hepatomas and in experimentally induced pancreatic carcinomas. For comparison purposes, the activity of another peptidase, dipeptidyl aminopeptidase IV (DPAP; EC 3.4.14.1), was assayed in the same tissues. GTP activity was high in fetal liver and hepatomas, but low in adult rat liver, with a marked sex difference, 3x higher in the female than in the male. In the pancreas, however, the activity of the enzyme was high in the adult but low in the fetus and in pancreatic carcinoma. There were no marked developmental changes or sex differences in pulmonary GTP activities. DPAP levels were low in fetal and neonatal liver and lung, they increased rapidly after birth and showed no sex differences in the adult. In Morris hepatomas and in pancreatic tumors the activity of DPAP was significantly lower than in normal adult liver and pancreas. These results suggest that measurements of GTP (and, to a lesser extent, DPAP) are remarkably suitable for the study of neoplastic cells and tissues. (Author abstract) (19 Refs)

50. DETECTION OF GAMMA GLUTAMYL TRANSPEPTIDASE IN THE LIVERS OF GERMFREE AND CONVENTIONAL RATS.

Pollard M, Luckert PH, Adams RA
Lobund Lab., Univ. Notre Dame, Notre Dame, IN, 46556
Lab Anim Sci; 32(2):147-149 1982

Germfree and conventional rats, 1-41 mo of age, were examined for gamma glutamyl transpeptidase in frozen sections prepared from their livers. This histochemical marker has been associated with early changes which develop following exposure to known carcinogenic agents. Positive gamma glutamyl transpeptidase markers were detected in 86% of germfree rats over 4 mo of age, and the gamma glutamyl transpeptidase foci were larger and more numerous as the animals aged, and the foci were prominent in rats with hepatic tumors. Gamma glutamyl transpeptidase foci were observed in 96% of livers from conventional rats at 11-20 mo of age. The agents responsible for induction of the gamma glutamyl transpeptidase foci in the liver were not identified. (Author abstract) (22 Refs)

51. ALPHA-FETOPROTEIN FORMATION AND BIOCHEMICAL CHANGES IN RAT LIVER DURING N-DIMETHYLNITROSAMINE-INDUCED CARCINOGENESIS.

Dolezhalova V, Stratil P, Simickova M, Cherni S, Rubenchik BL, Pliss MB, Gorban' GP
Inst. Clinical and Experimental Oncology, Brno, Czechoslovakia
Eksp Onkol; 4(1):51-55 1982

The effects of dimethylnitrosamine (DMNA) on the biosynthesis of alpha-fetoprotein (AFP) and liver metabolism were studied in male Wistar rats. Animals received a diet containing 0.01% DMNA for 20 wk. Extremely low blood levels of AFP were detected on wk 3-4, 25-26, and 35-36 after the initiation of DMNA administration. The low blood level of AFP was correlated with small number of hepatocytes containing AFP. AFP-positive hepatocytes were detected during the first wk after DMNA administration. The number of AFP-containing hepatocytes reached the max 30 wk after the initiation of the experiment, ie during the period of tumor development. The increase of deoxycytidylate deaminase activity was correlated with the increase of the proliferative activity of liver cells. Marked decrease of glucose-6-phosphatase was observed throughout the entire period of DMNA administration. DMNA did not change the rate of glycolysis or the activity of key glycolytic enzymes. (20 Refs) (In RUS)

52. DISTRIBUTION OF 5'-NUCLEOTIDASE DURING HEPATOCARCINOGENESIS INDUCED BY HEXACHLOROCYCLOHEXANE IN SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Babu KA, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(12):1159-1162 1981

Male inbred Swiss mice were fed 500 ppm of hexachlorocyclohexane (BHC) for 2, 4, or 6 mo and the livers were histochemically studied for the distribution of 5'-nucleotidase (5NT). After 2 mo, hepatocytes in the periportal area showed intense enzymatic activity. Activity in the nodular part increased compared with the nonnodular part. Tumor tissue always showed very strong 5NT activity compared with the nontumor tissue. Intercellular spaces showed strong 5NT activity. As time increased, the main changes in 5NT distribution were disappearance of 5NT from the cytoplasm (persisting even after tumor development), increase in 5NT activity in the nucleus (disappearing in well developed nodules and tumors), and gradual increase in 5NT activity on the plasma membrane and intercellular space. The change in activity during hepatocarcinogenesis may be associated with the functional and constitutional aspect of the plasma membrane. The absence of cytoplasmic activity of 5NT may be associated with complete disruption of ergestroplasm during carcinogenesis, excessive accumulation of glycogen in the cytoplasm, lysosomal damage, and repression of the gene responsible for synthesis of cytoplasmic 5NT. 5NT may be a specific indicator of hepatic diseases and tumors of the liver. (22 Refs)

53. NONHISTONE PROTEINS OF RAT LIVER TRANSFORMED BY NITROSODIETHYLAMINE.

Seits IF, Glebov AV
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 28(1):42-46 1982

Qualitative and quantitative content of nonhistone chromosomal proteins (NHP) from normal and nitrosodiethylamine-transformed rat liver was studied. An increase in the protein/DNA ratio in tumor chromatin, as compared with that of normal tissue, was established. NHP were extracted from the chromatin with 0.4 N N2SO4 and fractionated with two-dimensional polyacrylamide gel electrophoresis. Coomassie staining revealed more than 80 fractions with mol wt ranging 20-150 th. Some quantitative and qualitative differences in the patterns of NHP from normal and neoplastic tissues were observed. A conclusion is drawn that these differences may be related to structural and/or enzymatic components of NHP. (Author abstract) (17 Refs) (In RUS)

54. POLY(ADP-RIBOSYLATION) IN N,N-DIETHYLNITROSAMINE-TREATED MICE.

Shugart L, Chastain B, Holland JM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Biochem; 14(3):231-233 1982

C3H mice were treated with single injections of N,N-diethylnitrosamine (DEN: 35-100 mg/kg body wt, ip). Liver nuclei of the treated animals were examined for poly(ADP-ribose) and the conjugate enzyme poly(ADP-ribose) polymerase. The poly(ADP-ribose) content increased with time, showing a peak at about 4 hr post-injection and subsequently falling to pre-injection levels. This effect was dose dependent and was not observed in a control experiment which examined the nuclei of the kidney, a non-target tissue of DEN. The level of poly(ADP-ribose) polymerase also exhibited a transitory increase which was dose dependent. The return of poly(ADP-ribose) levels to the pre-injection level is probably not due to the accompanying loss of polymerase activity but instead to the transient induction of poly(ADP-ribose) glycohydrolase. DEN and other N-nitroso compounds are thought to exert their carcinogenicity via alkylation of DNA. Thus, the measurement of poly(ADP-ribose) and/or its polymerase may provide a basis for measuring DNA damage resulting from carcinogen exposure. (28 Refs)

55. ACID HYDROLASES AND TUMOR INVASION. RELATIONSHIP BETWEEN INTRACELLULAR DISTRIBUTION OF HYALURONIDASE, CATHEPSIN D AND ACID PHOSPHATASE, AND CELL PROLIFERATION, IN RAT LIVER AND DIETHYLNITROSAMINE-INDUCED HEPATOMA.

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Biol Cell; 42(2/3):97-102 1981

The distribution of acid phosphatase (E.C. 3.1.3.2) and cathepsin D (E.C. 3.4.4.23) activities in the subcellular fractions is different in diethylnitrosamine-induced hepatoma in rat from that in normal liver. These activities are decreased in lysosomes and increased in microsomes and in the soluble fraction; it is striking that hyaluronidase (E.C. 3.2.1.35) could be detected only as faint traces in the soluble fraction of the tumor cells. The time interval between two successive cell divisions in hepatoma was calculated to be between 50 and 175 hr. The time necessary for the dismantled lysosomal apparatus to be reconstituted is thus not available, as this process takes a much longer time (about 500 hr). The lysosomal enzyme depletion can thus result from these two concurring phenomena. Since the soluble fraction also contains the extracellular fluid, its increased acid phosphatase and cathepsin D proportions, along with its small hyaluronidase content, are in some way similar to the increase in hyaluronidase activity which we had observed in Walker carcinoma 256 interstitial fluid. These increases suggest the possible role of these enzymes in the invasive capacity of malignant tumors. (Author abstract) (30 Refs)

56. INHIBITION OF MITOCHONDRIAL PROTEIN SYNTHESIS DURING EARLY STAGES OF AFLATOXIN B1-INDUCED HEPATOCARCINOGENESIS.

Bhat NK, Emeh JK, Niranjan BG, Avadhani NG
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Cancer Res; 42(5):1876-1880 1982

Experiments were designed to determine the in vivo effects of a single 6-mg/kg dose of aflatoxin B1 on rat liver mitochondrial transcription and translation processes. With the use of intact hepatocytes and also a highly active mitoplast system for incorporation, it was observed that both mitochondrial transcription and translation activities are inhibited progressively even after 24 hr of carcinogen administration. Electrophoretic patterns of mitochondrial translation products show some qualitative changes during early periods of carcinogen administration. At later stages (greater than 12 hr), however, there is a general inhibition of many of the products, although by this time there is a qualitative and quantitative recovery in the synthesis of mitochondrial proteins imported from the cytoplasm. These results, along with the data showing considerably high levels of aflatoxin B1 binding to mitochondrial DNA suggest that mitochondrial genetic system is one of the direct targets during experimental carcinogenesis. (Author abstract) (31 Refs)

57. DISTURBANCES IN LYSOSOMAL ENZYME ACTIVITIES IN RATS FOLLOWING EXPERIMENTAL POSTRADIATION DISEASE.

Drozdz M, Piwowarczyk B, Olczyk K, Pikula-Zachara M
Zaklad Chemii Klinicznej, Instytut Farmakodynamiki i Analytiki Medycznej Sl. Am, ul. Borowkowa 24, 40-692 Katowice, Poland
Med Pr; 32(3):201-206 1981

The effect of irradiation (500 rads) on lysosomal enzyme activities in serum, leukocytes, liver, kidneys, lungs, and heart of 6-mo-old male Wistar rats was studied 30 days after irradiation. The increased acid phosphatase (AP), beta-glucuronidase and beta-acetylglucosaminidase activities in the tissues were indicative of the labilizing effect of irradiation on lysosomal membranes. Kidneys, lungs and liver were found to be the most radiosensitive organs. The AP activity showed the greatest increase in serum and leukocytes. The activities of all enzymes examined were reduced in hepatic lysosomes. (55 Refs) (In POL)

58. EFFECTS OF WHOLE-BODY IRRADIATION ON THE MICROSOMAL ENZYME SYSTEM AND ON CYTOCHROME P-450 OF RAT LIVER.

Zajac JM, Bernard P
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Enzyme; 27(1):19-24 1982

The rate of oxidative demethylation of ethylmorphine by preparations of microsomes from livers of male rats decreased following whole-body gamma-irradiation, reaching a minimum of 50% of the control value on the 5th or 6th day. The value of apparent Vmax changed markedly after irradiation when the Km value was unaltered. At the same time, the amount of cytochrome P-450 also decreased. For cytochrome P-450, the spectral change induced by ethylmorphine and the Ks value were not altered significantly. The reduced rate of oxidative demethylation may be explained partially by the reduction of cytochrome P-450 concentration. The radiation-induced peroxidation of microsomal lipids was also measured in this study. (Author abstract) (16 Refs)

59. BIOCHEMICAL CHANGES IN VINYL CHLORIDE POISONINGS. I. EFFECTS OF DIFFERENT VINYL CHLORIDE EXPOSURE CONDITIONS ON LIPID METABOLISM IN RATS.

Wronska-Nofer T, Parke M, Laurman W
Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(4):247-253 1981

The effect of inhaled vinyl chloride (VC: 50, 500 or 20,000 ppm, exposure time 1-10 mo) on lipid metabolism was studied in male Wistar rats. Significant increases in the serum triglyceride and phospholipid levels were found after 10-mo exposure to 20,000 ppm. Dose- and exposure time-dependence decreases were seen for cholesterol and especially for the triglyceride levels in liver but not in muscles, aortic wall and connective tissue. The findings indicate that disturbances in lipid metabolism play a minor role in the pathology of VC poisoning. (11 Refs) (In POL)

60. INDUCTION OF ORNITHINE DECARBOXYLASE IN COLON AND LIVER BY STARVATION AND REFEEDING: A COMPARISON OF EFFECTS ON TOTAL AND HOLOENZYME.

Stanley BA, Kazarinoff M
Div. Nutritional Sciences and Section Biochemistry, Molecular and Cell Biology, Div. Biological Sciences Cornell Univ., Ithaca, NY, 14853
Biochem Biophys Res Commun; 105(2):773-777 1982

Short-term starvation and refeeding induced both the total and holo-ornithine decarboxylase (ODC) levels in the colon of rats. After brief starvation alone, a significant decrease in total ODC was observed in the colon; there was no effect on colon holo-ODC. Similar effects on total ODC level were seen in the liver; neither starvation-refeeding nor starvation alone had any effect on liver holo-ODC levels. This is the first demonstration of the dietary induction of ODC in the colon. It is of interest to investigate whether this induction simply reflects a compensatory increase in general protein synthesis following starvation, or whether it represents a specific induction such as that observed during tumor promotion by chemical carcinogens. (18 Refs)

61. ALTERATIONS IN TISSUE GLUTATHIONE AND ANGIOTENSIN CONVERTING ENZYME DUE TO INHALATION OF DIESEL ENGINE EXHAUST.

Chaudhari A, Dutta S
Dept. Medicine, UCLA Sch. Medicine, Los Angeles, CA, 90024
J Toxicol Environ Health; 9(2):327-337 1982

Biochemical changes in rat and guinea pig lung and extrapulmonary organs after exposure to diesel engine exhaust (DEE) were investigated. Rat and guinea pig lung, liver, and heart showed no significant changes after exposure to low levels (750 ug/cubic meter for 12 wk) of DEE. Higher doses (6 mg/cubic meter for 2-8 wk) produced varying increases in glutathione (GSH) levels of lung and heart tissue in rats. Hepatic GSH levels showed a slight increase but ultimately decreased over the same test period. Rat serum angiotensin converting enzyme (ACE) activity increased, while pulmonary ACE activity decreased, when rats were exposed to the higher dosage. Exposure to DEE causes lung and extrapulmonary effects in laboratory animals. (35 Refs)

62. MODIFICATIONS IN ALPHA 2U GLOBULIN GENE STRUCTURE, TRANSCRIPTION, AND MRNA TRANSLATION IN HEPATOMAS.

Nakhasi HL, Lynch KR, Dolan KP, Unterman R, Antakly T, Feigelson P
(c/o Feigelson) Dept. Biochemistry, Inst. Cancer Res., Columbia Univ., New York, NY, 10032
J Biol Chem; 257(6):2726-2729 1982

Alpha 2u globulin synthesis ceases when a liver cell becomes malignant. We have compared the structure and transcription of the alpha 2u globulin genes in Morris hepatomas 5123D and 7793 with that of normal hepatic genes using alpha 2u globulin cDNA as a hybridization probe. No alpha 2u globulin mRNA was detected in hepatoma 7793 by cell-free translation, Northern blot, or Rot analysis. In hepatoma 5123D, however, a small number of alpha 2u globulin RNA sequences were detected by Northern blot and Rot analysis, but this RNA was not detectably translationally active either in vivo or in an in vitro cell-free translational system. No structural differences between normal liver and the hepatoma alpha 2u globulin genes were observed by Southern blot analysis of genomic DNA digested with restriction endonucleases Pst I, Bam HI, or Ava I. However, a general demethylation of cytosine residues in the alpha 2u globulin genes of hepatomas has been found using the restriction enzyme Hha I and the isoschizomeric pair of restriction enzymes Msp I and Hpa II. Therefore, loss of the alpha 2u globulin phenotype in these hepatomas is accompanied by extensive demethylation of DNA sequences within and/or immediately flanking the alpha 2u globulin genes. (Author abstract) (29 Refs)

63. POLYSOMAL POLYADENYLATED RNA AND ALBUMIN MESSENGER RNA IN MASTOMYS LIVER AND IN A CHEMICALLY INDUCED HEPATOCELLULAR CARCINOMA.

Krieg L, Krause-Leipholdt D, Wayss K, Volm M
Institut fur Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld, D-6900 Heidelberg, W. Germany
Cancer Res; 42(5):1986-1993 1982

A hepatocellular carcinoma line (H78) was established from a primary liver tumor induced in Mastomys natalensis by a single administration of dimethylnitrosamine. Six to 8 mo after transplantation (passages 5 to 7), well-differentiated tumors, still containing glycogen-storing cells, were isolated and used for the preparation of RNA. Polysomal polyadenylated RNAs from Mastomys liver and from the H78 tumor line were then compared by hybridization kinetics. Total kinetic complexities were 6.6 x 10(9) and 6.3 x 10(9) daltons for liver and tumor, respectively. Complexities of the high and middle abundant class were reduced in the hepatoma. Heterologous hybridization reactions revealed that, in terms of RNA mass, all or most of the polysomal polyadenylated RNA present in the liver was also present in the tumor and vice versa. However, shifts in the relative abundance of messenger RNA sequences were detected. In contrast to most other transplanted hepatomas, H78 has approx the same content of albumin messenger RNA on its polysomes as has untreated liver. (Author abstract) (44 Refs)

64. SENSITIVITY TO RNASE TREATMENT OF RIBOSOMES AND RRNA FROM NORMAL RAT LIVER AND NOVIKOFF HEPATOMA.

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Br J Cancer; 45(1):140-143 1982

Biochemical assays were used to verify whether fresh ribosomes isolated from Novikoff hepatomas differ from those of normal Wistar rat liver in sensitivity to RNase and capacity to bind basic dyes. Ribosomal RNA (rRNA) was extracted from normal and tumor ribosomes by the dodecyl sulfate-phenol method. The amounts of RNA hydrolyzed by RNase were expressed as the percentage of total RNA (determined by complete hydrolysis of 5 absorbance units of ribosome suspension or rRNA soln after incubation with 5 ml 10% perchloric acid for 1 hr at 25 C) Nearly max hydrolysis was observed in both normal and tumor preparations after 1 hr treatment. Tumor ribosomes incubated with RNase at a final concentration of 20 nanog/ml showed a linear rate of RNA degradation to 6% and 8% after 20 and 30 min, respectively. The same treatment had little effect on ribosomes from normal liver; RNase concentration had to be increased 10-fold to obtain the rates of hydrolysis seen with tumor ribosomes. The ribosomes from tumor preparations were approx 5x as sensitive to pancreatic RNase treatment as those of normal livers. Basic changes occurring in the liver ribosome as a result of neoplastic transformation may be responsible for both the increased dye-binding of tumor ribosomes and the greater sensitivity to RNase. (13 Refs)

65. ALPHA-FETOPROTEIN SYNTHESIS IN PRIMARY CULTURES OF HEPATOCYTES OF ADULT MICE.

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Lab. Immunochemistry and Tumor Diagnosis, All-Union Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 92(1):55-58 1982

To determine whether the biosynthesis of alpha-fetoprotein (AFP) is associated with local disturbances of interhepatocyte contacts, AFP and albumin synthesis were studied in primary cultures of hepatocytes of adult C57Bl/6J, SWR, BALB/c, and (C57BL/6J x CBA)F1 mice. Immunoperoxidase staining showed the presence of AFP-containing hepatocytes starting from day 3 of culturing. Significant numbers of AFP-containing hepatocytes were observed on day 5. AFP synthesis in the cultured C57BL/6J hepatocytes was similar to that in the cultured SWR hepatocytes, while in vivo AFP synthesis in regenerating liver of the C57BL/6J mice was 10x lower than that in the regenerating liver of the SWR mice. (14 Refs) (In RUS)

66. SERUM-ALPHA1-FETOPROTEIN AND SERUM FERRITIN IN LIVER TUMORS.

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Wien Klin Wochenschr; 94(4):105-108 1982

Values of serum ferritin (SF) were evaluated in 22 patients (16 men, 6 women; 24-78 yr old) with histologically confirmed primary hepatic cancer (PHC); 11 patients had malignant hepatoma (MH) in liver without cirrhosis, 11 had MH associated with different hepatic pathologies; and in 25 patients (13 men, 12 women; 35-78 yr old) with histologically confirmed hepatic metastases (HM) from different primary cancers (12 large intestine, 5 pancreas, 3 stomach, and others). Radioimmunoassay was used for determination of alpha-1-fetoprotein (AFT) with normal values up to 9 nanog (ng)/ml. Heterologous antibody system was used for the determination of SF with the normal values 29-343 ng/ml (measured on 396 healthy controls). AFP values were elevated in 95.4% of PHC patients, but only 81.8% had values greater than 174 ng/ml, which were considered suspicious for PHC. SF values were elevated in 77.2% of PHC patients. Four of PHC patients had increased values of SF, although AFT values were low. SF values were elevated in 88% of HM patients, while AFT values were elevated only in 28%. Using both tests (SF and AFP) diagnosis of hepatic cancer would be increased. Elevated values for SF cannot differentiate between PHC and HM. (19 Refs) (In GER)

67. PLASMA INSULIN AND C-PEPTIDE DYNAMICS IN VARIOUS DISEASES OF THE LIVER.

Obayashi M, Kawakami H, Hashimoto H, Nakanishi T, Miyoshi A
First Dept. Internal Medicine, Hiroshima Univ. Sch. Medicine, Hiroshima, Japan
Naika Hokan; 28(11):323-337 1981

Changes in blood sugar (BS) and immuno-reactive insulin (IRI) dynamics of patients with various liver diseases were compared with those in normal adults and patients with primary diabetes. Oral glucose tolerance tests (OGTT; 50 g glucose) were performed in 157 cases (14 acute hepatitis, 30 chronic hepatitis, 62 liver cirrhosis, 28 primary hepatic cancer, 11 metastatic liver cancer, and 12 alcoholic hepatopathy) and allergin tolerance tests (ATT) were performed in 51 cases (35 liver cirrhosis, 10 primary hepatoma, and 6 metastatic hepatoma). Prior to and following the OGTT, IRI levels were 09.0 +-7.3 microunits(uU)/ml (before OGTT), 34.7 +-33.7 (min 30), 54.1 +-45.7 (min 60), 54.2 +-39.2 (min 120), and 26.3 +-15.5 (min 180) in the patients with primary hepatic cancer and were 6.9 +-4.1 uU/ml (before), 21.7 +-13.7 (min 30), 30.7 +-21.5 (min 60), 32.6 +-31.8 (min 120), and 21.6 +-18.6 (min 180) in the patients with metastatic liver cancer; all of the IRI levels in the primary liver cancer patients were higher than those of the metastatic cancer patients. Although the BS curves of the metastatic liver cancer patients were higher than those of the controls, IRI levels were markedly lower, and the IRI levels of both groups of liver cancer patients at min 30 after the OGTT were significantly lower than those of the normal controls. IRI levels of the patients who had primary liver cancer with complications of cirrhotic changes were significantly lower than those of the patients with cirrhosis alone. (29 Refs) (In JPN)

68. FERRITIN LEVELS AND CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH SOLID TUMORS.

Celada A, Barnet M, Aguado MT, Cruchaud A, Lambert PH
Div. Hematology RM 10, Dept. Medicine, Univ. Washington, Seattle, WA, 98195
Bull Cancer (Paris); 69(1):22-27 1982

The level of ferritin and circulating immune complexes (IC) were measured in 53 patients with solid tumors and metastasis using C1q binding assay and the conglutinin binding assay. The level of circulating IC was increased in patients (p less than 0.001) as compared to the controls. Ferritin level was increased in both male and female patients (p less than 0.001), even when the ferritin value was corrected by the aspartic transaminase value, to take hepatic damage into account. Ferritin was not found to be an important component of immune complexes as IC ferritin did not exceed 2% of total serum ferritin in the 10 patients that were investigated. These results suggest that ferritin levels and circulating IC are increased in patients with solid tumors and metastasis, but that these two parameters are not correlated. (Author abstract) (29 Refs)

69. A CLINICAL EVALUATION OF SERUM ALPHA-1-ANTICHYMOTRYPSIN LEVELS IN LIVER DISEASE AND CANCERS.

Matsuzaki S, Iwamura K, Itakura M, Kamiguchi H, Katsunuma T
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Gastroenterol Jpn; 16(6):582-591 1981

The serum levels of alpha-1-antichymotrypsin (ACT) were studied in 168 patients with various liver diseases and cancers in conjunction with other liver function tests, serum sialic acid, AFP and CEA. The ACT levels in acute viral hepatitis and chronic hepatitis were not significantly altered compared with the normal level (220 +-40 ug/ml), although the level was slightly increased or decreased temporarily during the acute phase of the former. In liver cirrhosis, the mean level was significantly lower than the normal in spite of the absence of signs of hepatic decompensation (168 +-51 ug/ml, p less than 0.001). In contrast to cirrhosis, the levels were increased to various extents in 65% of cases with hepatoma, in spite of the association of liver cirrhosis in the majority of them. Much higher levels were observed in all cases of metastatic liver cancers and cancers of the pancreas and the biliary tract. The elevations were observed even in cases without the increase of AFP or CEA. Both in cirrhosis and cancers, ACT levels were not correlated with any of serum bilirubin and serum enzyme activities, but were positively correlated with the levels of plasma fibrinogen and serum sialic acid. The measurement of serum ACT level can be taken advantage of for the diagnosis and monitoring of liver cirrhosis and liver cancers, particularly of hepatoma without AFP elevation. (Author abstract) (18 Refs)

70. ANALYSIS OF ALKALINE PHOSPHATASE ISOENZYMES IN THE URINE.

Tikhonov VP, Kolupaeva GI, Mal'tseva GI
Dept. Therapy, Medical Inst., Volgograd, USSR
Lab Delo; (2):92-96 1982

Diagnostic value of determination of alkaline phosphatase (AP) isoenzymes in the urine was studied in 72 patients with diabetes mellitus, 18 with glomerulonephritis, 21 with chronic pyelonephritis, 8 with primary and metastatic liver cancer, 12 with liver cirrhosis, 4 with stomach neoplasms without liver metastases, and 1 with hypernephroma. Marked elevation of the fast fraction I was detected in the patients with liver and kidney diseases. (12 Refs) (In RUS)

71. NO EVIDENCE FOR POST-TRANSCRIPTIONAL CONTROL OF ALBUMIN AND ALPHA-FETOPROTEIN GENE EXPRESSION IN DEVELOPING RAT LIVER AND NEOPLASIA.

Nahon JL, Gal A, Frain M, Sell S, Sala-Trepat JM
Laboratoire d'Enzymologie, CNRS, 91190 Gif-sur-Yvette, France
Nucleic Acids Res; 10(6):1895-1911 1982

Rot analysis of hybridization data using highly labeled alpha-fetoprotein (AFP) and albumin (32P)cDNA probes has been used to quantitate AFP and albumin mRNA sequences in RNA preparations from different subcellular fractions of developing rat liver and Morris hepatoma 7777. In addition, size analysis of these mRNA sequences has been carried out by electrophoretic fractionation on agarose gels containing methylmercury hydroxide and hybridization to radioactive cloned albumin and AFP cDNA probes. In all the tissues examined (fetal, newborn and adult rat liver, and hepatoma 7777) most of the albumin and AFP mRNA sequences were found associated with the polysomes as mature mRNA molecules; less than 2% of these sequences were present in the nuclear or the nonpolysomal cytoplasmic compartments. The number of AFP mRNA molecules was found to decrease in parallel in all the cellular compartments during rat liver development. In Morris hepatoma 7777 the content of albumin mRNA was considerably decreased in all the cellular fractions as compared to normal liver. These results demonstrate that post-transcriptional control mechanisms leading to an accumulation of non-functional mRNA molecules are not implicated in the changes of expression of albumin and AFP genes during rat liver development and neoplasia. (Author abstract) (47 Refs)

72. STRUCTURE OF O-GLYCOSIDICALLY LINKED SUGAR UNITS FROM PLASMA MEMBRANES OF AN ASCITES HEPATOMA, AH 66.

Funakoshi I, Yamashina I
Dept. Biological Chemistry, Kyoto Univ., Sakyo-ku Kyoto 606, Japan
J Biol Chem; 257(7):3782-3787 1982

The structure of O-glycosidically linked oligosaccharides from plasma membranes of AH 66 ascites hepatoma cells have been determined. Glycopeptides were prepared from a Triton X-100 extract of the cells by pronase digestion. From the digest, the glycopeptide containing O-glycosidically linked oligosaccharides was isolated by gel filtration and electrophoresis on a cellulose acetate block. The oligosaccharide chains were isolated as reduced oligosaccharides by treating the glycopeptide with alkaline borohydride. Neutral and acidic oligosaccharides were separated on a column of Dowex 1, and then each of them was further fractionated by gel filtration on Sephadex G-25 (super-fine), high voltage paper electrophoresis, and paper chromatography. One reduced monosaccharide, three neutral, and five acidic reduced oligosaccharides were isolated. On the basis of carbohydrate compositions, mass spectra of permethylated oligosaccharides, methylation analysis, and exoglycosidase digestion, their structures were deduced. (40 Refs)

73. TURNOVER OF MITOCHONDRIAL INNER MEMBRANE PROTEINS IN HEPATOMA MONOLAYER CULTURES.

Hare JF, Hodges R
Dept. Biochemistry, Sch. Medicine, Oregon Health Sciences Univ., Portland, OR, 97201
J Biol Chem; 257(7):3575-3580 1982

The degradation rates of inner mitochondrial membrane proteins were examined in serum-deprived hepatoma cultures. In those nonproliferating cells, the degradation of composite mitochondrial proteins was a first order process with a half-life of 34 hr. The half-lives of specific inner mitochondrial membrane polypeptides were determined by examining the 3H/35S of isolated polypeptides from cells given [3H]methionine and [35S]methionine pulses, respectively, before and after a 2-day chase period. The 33 most abundant polypeptides resolved on a bidirectional polyacrylamide gel system showed half-lives ranging from 20 to 100+ hr. The 15 polypeptides translated on mitochondrial ribosomes in the presence of inhibitory concentrations of cycloheximide also displayed heterogeneous rates of degradation (t 1/2 = 35-100+ hr). None of the isolated adenosine triphosphatase (coupling factor F1) or immunoprecipitated cytochrome c oxidase subunits were significantly turned over during the case period. Five of eight cytochrome b-c1 complex subunits, however, were turned over significantly more rapidly (t 1/2 = 39-42 hr) than the other three (t 1/2 = 94+ hr). The results demonstrate heterogenous degradation rates for inner membrane polypeptides, extending in some cases to those within the same respiratory complex. (Author abstract) (49 Refs)

74. PARTIAL PURIFICATION FROM HEPATOMA CELLS OF AN INTRACELLULAR SUBSTANCE WHICH MEDIATES THE EFFECTS OF INSULIN ON PYRUVATE DEHYDROGENASE AND LOW KM CYCLIC AMP PHOSPHODIESTERASE.

Parker JC, Kiechle FL, Jarett L
Dept. Pathology and Lab. Medicine, Univ. Pennsylvania Sch. Medicine, Box 671, 3400 Spruce St./G1, Philadelphia, PA, 19104
Arch Biochem Biophys; 215(1):339-344 1982

An enzyme-stimulating factor was isolated from hepatoma cells. The factor stimulated pyruvate dehydrogenase (PD) and low Km cyclic AMP phosphodiesterase in a dose-dependent fashion. PD stimulation was sodium-sensitive. The factor was similar to the second messenger of insulin derived from other cell types in acid stability, mol wt, insulin-dependent generation, and elution from the anion-exchange resin AG 1-X8 at an ionic strength of 0.4 M. (21 Refs)

REVIEWS AND OTHER RELATED STUDIES

75. ASPECTS OF RESEARCH STUDIES ON LIVER CARCINOMA.

Zhen Y

Shanghai Inst. Cell Biology, Academia Sinica, Shanghai, People's Republic of China

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Studies with human liver carcinoma (HLC) and rat hepatoma are summarized. In vitro cultured HLC cell lines, fetal antigens in HLC, localization of surface and core antigen of hepatitis B virus in human hepatoma, cell-mediated cytotoxicity and immune RNA studies in human hepatoma, and experimental hepatoma research are discussed. A transplantable rat hepatoma was established by feeding Wistar rats with diethylnitrosamine in drinking water. The hepatoma exhibited fetal characteristics, including alpha-fetoprotein production, fetal isozyme expression, and the presence of membrane-associated fetal antigen. Research using these model systems and liver material derived from animals during carcinogenesis and from regenerated and fetal livers is described. (19 Refs)

76. CANCER RESEARCH IN THE PEOPLE'S REPUBLIC OF CHINA AND THE UNITED STATES OF AMERICA. EPIDEMIOLOGY, CAUSATION AND NEW APPROACHES TO THERAPY. PROCEEDINGS OF A CONFERENCE HELD IN NEW YORK, 28-29, MARCH, 1980.

Marks PA

Memorial Sloan-Kettering Cancer Center, New York, NY

Cancer Research in the People's Republic of China and the United States of America. Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. New York, Grune and Stratton, 273 pp., 1981.

Cancer (CA) epidemiology, causation, diagnosis, and therapy are discussed. An overview of CA research, needs and opportunities of evolving perspectives on the epidemiology of CA, a national survey of CA mortality in China, geographic patterns of CA in the United States, and progress of CA epidemiology in China are presented. The study of a virus-related protein in human breast CA, the nature of CA cells, potential carcinogens in the diet of individuals at high risk for esophageal CA, association of the Epstein-Barr virus with nasopharyngeal carcinoma (CR), aspects of research studies on liver CR, the mechanisms of action of carcinogens and tumor promoters and their relevance to CA prevention, immunological studies of esophageal CA in man, and nasopharyngeal CR epidemiology, risk factors and screening for early detection are presented. Recent progress in antineoplastic drug research in China, gene amplification in methotrexate resistant cells, and studies on harringtonine as a new antitumor drug are discussed. Advances in the study of CA epidemiology, biology, and therapy in the laboratories are offering new options for the prevention and treatment of CA. The substantive exchanges among scientists of these countries provide data useful for CA research and treatment. (365 Refs)

77. HEPATOTOXICITY OF CHEMOTHERAPEUTIC AGENTS.

Perry MC

Div. Hematology/Medical Oncology, Dept. Medicine, Univ. Missouri Health Sciences Center, Columbia, MO, 65212

Semin Oncol; 9(1):65-74 1982

Hepatotoxicity of chemotherapeutic agents is discussed and strategies for amelioration are reviewed. Hepatotoxins include nitrosoureas, antimetabolites, antibiotics, and enzymes used in chemotherapy. Some hepatoxicities are evident through elevated SGOT, SGPT, lactate dehydrogenase (LDH), alkaline phosphatase, and bilirubin levels, or by induction of jaundice. Mithramycin is the most hepatotoxic of commercially available agents; SGOT and LDH levels are elevated in virtually all patients receiving the drug. Several chemotherapeutic agents, among them 5-fluorouracil, mitomycin C, bleomycin, and procarbazine, are metabolized in the liver. Adjustments in dosage sometimes must be made to compensate for hepatic dysfunction. A dose modification scheme is proposed in which levels of bilirubin and SGOT are used as indicators of liver function to determine the appropriate dose. Combination chemotherapy has the potential for increased toxicity concomitant with increased tumor kill rates. Liver function tests should be performed prior to chemotherapy, and liver function should be monitored. Liver biopsy may be required to determine whether drug or liver disease is responsible for observed dysfunction before management can be planned. (58 Refs)

78. CAUSES OF LEUKEMIAS AND CANCER: RECENT PROGRESS.

Bernard J

bd. de Perolles 53, 1700 Fribourg, Switzerland

Rev Med Suisse Romande; 102(1):95-103 1982

Roles of viruses, radiation, and toxic chemical substances in the development of cancer are discussed. Burkitt's lymphoma (BL), a B-cell lymphoma predominantly localized in facial bones and found most frequently in certain areas of Africa, was one of the first cancers to be related to a virus, Epstein Barr virus (EBV). EBV virus and its antibodies are found in BL patients. EBV virus, the infective agent in mononucleosis, has been shown to cause BL in marmosets. BL shows high correlations with geographic areas with levels of malaria, with chromosome translocation 8:14, and with lower socioeconomic groups. Viruses have also been implicated in cervix cancer (herpes virus), liver cancer (hepatitis B), and Hodgkin's disease. Evidence of radiation-induced cancers has been gained from studies of physicians, radiologists, and scientists exposed to radiation and of Hiroshima survivors. The relationship between radiation and cancer development is significant but varies among individuals. Dietary factors, such as tobacco (lung, bladder, and digestive cancers), alcohol (cirrhosis and liver cancer), and diet in general (high lipid diet and breast cancer) have been related to increased incidences of cancer. Leukemia has been observed in Hodgkin's disease patients treated with chemotherapy. A high incidence of lymphomas has been noted in patients who have undergone organ transplants. The role of heredity and geography in the etiology of cancer is discussed. (no Refs) (In FRE)

79. THE MENOPAUSE: BENEFITS AND RISKS OF ESTROGEN-PROGESTOGEN REPLACEMENT THERAPY.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Fertil Steril; 37(4):457-474 1982

The benefits of cyclic estrogen-progestogen administration for the relief of vasomotor symptoms, urogenital atrophy, psychosomatic complaints, osteoporosis, and possibly cardiovascular risks are reviewed. Risks of endometrial cancer and hyperplasia, breast cancer, thromboembolic phenomena, and gallbladder disease are discussed. The benefits of appropriate postmenopausal estrogen therapy seem to outweigh the risks for many women, although not all need such therapy; some with significant levels of endogenous estrogen may need progestogens to reduce the risk of endometrial cancer. (90 Refs)

80. METHOD OF ANALYSIS OF MONOTONE DOSE-RESPONSE PROBABILITIES AFTER LONG-TERM EXPOSURE TO A TOXICANT.

Scott BR
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87185
Health Phys; 42(3):305-315 1982

A nonparametric hazard-function (HP) method for generating monotonically increasing incidence vs dose curves after long-term exposure to a toxic agent (eg radiation or chemical carcinogens) is described in detail in this paper. Here, incidence refers to the response-probability estimate that is adjusted for competing risks. The maximum likelihood principle was used to arrive at an appropriate point estimate of the cumulative hazard function (ie the negative natural logarithm of the proportion of nonresponders) and the response probability for an array of doses that depends on the data set to be analyzed. The resultant point estimates can be used to develop or select an appropriate model for risk vs dose assessment. As an example of the application of the HF method, data for liver neoplasms caused by long-term exposure of mice to 2-acetylaminofluorene and data for radiation pneumonitis and pulmonary fibrosis caused by long-term exposure of dogs to ionizing radiation are analyzed. (Author abstract) (15 Refs)

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1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
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Side Eff Drugs Annu; (5):278-284 1981

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Elis J
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Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, 1 e Helmerstraat 104, 1054 EG Amsterdam, The Netherlands
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15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
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Adv Genet; 21:1-52 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
Bickers DR
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18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
Rom WN, Lee JS, Craft BF
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Scand J Work Environ Health; 8(1):1-19 1982

20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
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JOM; 24(4):305-314 1982

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No affiliation given
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Kotin P
4505 South Yosemite, 339, Denver, CO, 80237
JOM; 24(4):290-294 1982

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Hull LA
104 Depot St., New Sharon, IA, 50207
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24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Veremeenko KN
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Eksp Onkol; 4(1):3-7 1982
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25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
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Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
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Williams GM
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Lab Invest; 46(3):352-354 1982

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27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
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Cancer. An Introduction. New York, Oxford University Press, 271 pp., 1981.

30. CANCER 1980: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS.
Clark RL
Univ. Texas System Cancer Center, M.D. Anderson Hosp and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9):1739-1745 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. MALNUTRITION, LIVER DAMAGE, AND CANCER.

Grasso P

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Nutr Cancer; 3(2):103-108 1981

There is no clear indication that malnutrition, per se, is a principal cause of cancer in man, but the prevalence of liver cancer in areas where malnutrition exists supports this hypothesis. Liver damage and liver cancer have been induced in laboratory rats by diets consisting of peanut meal and proteins deficient in some essential amino acids. However, liver damage, but not cancer, was produced when the diets contained no peanut meal but consisted of a mixture of amino acids deficient in methionine and cysteine, so that it is possible that aflatoxin, a contaminant of peanut meal, may have been responsible for the malignancies seen in the earlier experiments. Liver cancer develops in a high proportion of mice allowed to feed ad libitum or given a diet containing a high proportion of fat (groundnut oil) or protein (casein). Dietary restriction reduced the incidences of this cancer. This finding lends some support to current thinking that diet may be a factor in the development of cancer in man. (Author abstract) (23 Refs)

2. VINYL CHLORIDE EXPOSURE AND MORTALITY AMONG GERMAN CHEMICAL WORKERS IN COMPARISON WITH MORTALITY AMONG NONEXPOSED WORKERS AND PVC MANUFACTURING WORKERS.

Greiser E, Reinl W, Weber H

(c/o Reinl) Gurlittstrasse 53, D-4000 Dusseldorf, W. Germany

Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(2):44-62 1982

A historical prospective study compared mortality among workers in the German chemical industry. All workers studied were males of German or Austrian nationality. Three cohorts included 7,021 workers exposed to vinyl chloride monomer (VCM) and polyvinyl chloride (PVC), 4,910 chemical workers not exposed to VCM or PVC, and 4,007 workers exposed to PVC. Follow-up rate at the end of the study was approx 90%. The total male population of West Germany for corresponding yr served as controls. Standardized mortality ratios (SMR) showed no 'healthy worker effect' for PVC or VCM/PVC workers. SMR for malignant hepatic tumors was significantly higher than for controls. The increase was dose-dependent. Nonexposed workers showed a small increase in SMR for hepatic malignancies. VCM/PVC worker showed a significantly increased SMR for lymphatic and hematopoietic malignancies. PVC workers showed an increased SMR for malignant brain tumors. VCM/PVC, PVC, and nonexposed workers all showed an increased SMR for ischemic heart disease compared with controls. Because of long latency time for development of malignant tumors and the increasing incidence of hepatic hemangiosarcomas, additional follow-up studies of VCM/PVC workers are urged. (20 Refs) (In GER)

TUMOR INDUCTION IN ANIMALS

3. FEEDBACK CONTROL OF CHOLESTEROL BIOSYNTHESIS IN MICE FED THE LIVER CARCINOGENS BENZIDINE AND 2-ACETYLAMINOFLUORENE.

Depass LR, Morris MD

Bushy Run Res. Center, Carnegie-Mellon Univ., 4400 Fifth Ave., Pittsburgh, PA, 15213

Cancer Biochem Biophys; 6(1):47-51 1982

Dietary feedback control (DFC) of hepatic cholesterol synthesis is absent or defective in hepatomas of trout, mouse, rat and man. DFC has also been shown to be defective in rats fed several liver carcinogens including 2-acetylaminofluorene (AAF). These studies have led to the hypothesis that loss of normal DFC is an early and consistent event in the development of liver cancer. To determine whether DFC was defective in 'precancerous' mouse livers, we fed the liver carcinogens AAF (0.05% in chow) and benzidine (0.02% in drinking water) to male BALB/c and C57BL/6 mice for 3 or 6 weeks. We measured sterol synthesis as incorporation of 2-14C-acetate into digitonin-precipitable sterols by liver slices. DFC was tested by adding 2% cholesterol to the diet for 3 days prior to sacrifice. Benzidine (but not AAF) treatment enhanced sterol synthesis in C57BL/6, but not in BALB/c, mice. However DFC was normal in both strains with either carcinogen. The results indicate that defective DFC is not a consistent early finding in animals fed liver carcinogens. Since defective DFC has been a consistent finding in AAF-fed rats, additional research is needed to determine whether the same genetic factors which determine susceptibility to chemically-induced neoplasia are also important in influencing DFC in carcinogen-fed animals. (Author abstract) (32 Refs)

4. EXPERIMENTAL STUDY OF THE BIOLOGICAL EFFECTS OF SMALL CONCENTRATIONS OF A MIXTURE OF DIMETHYLNITROSAMINE, DIMETHYLAMINE, AND NITROGEN DIOXIDE.

Prusakov VM, Benemanskii VV, Leshchenko ME, Katul'skii IuN

No affiliation given

Gig Sanit; (3):8-11 1982

The carcinogenic effect of combined exposure to a mixture of dimethylnitrosamine (DMNA), dimethylamine (DMA), and nitrogen dioxide (NDO) was studied in random-bred albino rats. The animals were subjected to a chronic, around-the-clock inhalation exposure to DMNA alone (0.07-0.66 mg/cubic meter) or in combination with DMA and NDO. The experiment continued for 1 yr. Analysis of the toxic effects DMNA alone and in combination with DMA and NDO showed wave-like changes in the RBC, WBC, and platelet counts. Exposure to DMNA resulted in a dose-dependent increase of liver and kidney tumors. Significant increase of the tumor yield after exposure to DMNA alone was observed for the doses of 19.2-44.2 mg/rat. DMNA in combination with DMA and NDO induced tumors at doses of 3.9-16.7 mg/rats. These findings are indicative of the synergism between DMNA, DMA, and NDO with respect to the carcinogenic activity and additive effect with respect to the general toxicity. (3 Refs) (In RUS)

5. LIVER TUMORS INDUCED BY A NEW BETA-ADRENORECEPTOR BLOCKING AGENT IN FEMALE RATS.

Ragnotti G, Presta M, Riboni L, Zavanella T

Patologia Generale (EULO), Inst. Biomedical Sciences, Univ. Milan, Via Valsabbina 19, 25100 Brescia, Italy

JNCI; 68(4):669-672 1982

A newly synthesized beta-adrenoreceptor blocking agent, DL-1-(2-nitro-3-methyl-phenoxy)-3-tert-butylamino propan-2-ol (ZAMI 1305), administered intragastrically for 6 mo induced hepatocellular carcinomas in female outbred Wistar rats in a dose-dependent fashion but was harmless to the livers of male outbred Wistar rats. Experiments with castrated animals confirmed the dependence of the carcinogenic effect of ZAMI 1305 on the hormonal status of the rat. When an isomer of ZAMI 1305, DL-1-(2-nitro-5-methyl-phenoxy)-3-tert-butylamino propan-2-ol (ZAMI 1327), and DL-practolol, which have pharmacologic activities similar to those of ZAMI 1305, were administered by the same experimental technique as used for ZAMI 1305, no liver tumors appeared either in male or female rats. (Author abstract) (16 Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

6. DIETARY MODIFICATION OF METABOLISM AND TOXICITY OF CHEMICAL SUBSTANCES - WITH SPECIAL REFERENCE TO CARBOHYDRATE.

Nakajima T, Koyama Y, Sato A

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Biochem Pharmacol; 31(6):1005-1011 1982

Rats were fed various test diets only on the day before sacrifice or every day for 3 wk prior to sacrifice in order to assess the effects of protein (casein), fat (a mixture of olive and corn oils) and carbohydrate (sucrose) on the liver mixed-function oxidase activity. The activity was determined by measuring metabolic rates of eight volatile hydrocarbons, ie, benzene, toluene, styrene, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethylene, and trichloroethylene. Contrary to the general belief, it was found that carbohydrate, not protein or fat, regulates the metabolism of these hydrocarbons; a diet which was deficient in carbohydrate remarkably enhanced the metabolism irrespective of protein and fat contents in the diet. This conclusion was confirmed by employing two types of diet, one in which the carbohydrate was replaced by an isocaloric amount of protein or fat (thus keeping total calories of each diet constant) and the other in which the carbohydrate content was varied with protein and fat contents fixed (total calories of each diet differed from others according to the carbohydrate content). In accordance with this, dietary carbohydrate intake also exerted a remarkable influence on the hepatoxocity of carbon tetrachloride which needs to be metabolically activated to become cytotoxic; the smaller the intake, the more severe the liver injury. (Author abstract) (28 Refs)

7. GLUTATHIONE S-TRANSFERASE ACTIVITY: ENHANCEMENT BY COMPOUNDS INHIBITING CHEMICAL CARCINOGENESIS AND BY DIETARY CONSTITUENTS.

Sparnins VL, Venegas PL, Wattenberg LW

Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455

JNCI; 68(3):493-496 1982

Benzyl isothiocyanate, beta-naphthoflavone, coumarin, alpha-angelicalactone, disulfiram, indole-3-carbinol and indole-3-acetonitrile induced increased (GSH) glutathione S-transferase activity in the liver and small intestine in female ICR/Ha mice. All seven compounds are inhibitors of chemical carcinogenesis. In additional work, several dietary constituents increased GSH S-transferase activity. Consumption of diets containing dried powdered preparations of brussel sprouts, cabbage, coffee beans, or tea leaves resulted in increased GSH S-transferase activity. Mice fed an unrefined diet (Purina Rat Chow) had a higher GSH S-transferase activity than those fed a semipurified diet. The results of the present study indicated that the composition of the diet can alter the activity of an important enzyme system having the capacity to detoxify chemical carcinogens. (Author abstract) (28 Refs)

8. PROMOTIVE EFFECTS OF STEROIDS AND BILE ACIDS ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE.

Cameron RG, Imaida K, Tsuda H, Ito N

(c/o Ito) First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Cancer Res; 42(6):2426-2428 1982

The ability of four steroids and three bile acids to promote the appearance of hyperplastic foci and hyperplastic nodules initiated by diethylnitrosamine (DEN) in the liver of male Fischer rats was tested and compared with that of the known promoter phenobarbital (PB, 0.05%) as a standard value. Two weeks after a single dose of 200 mg of DEN per kg, the animals were exposed to test chemicals for 10 weeks. At 4 weeks following DEN, all treatment groups were subjected to partial hepatectomy. Of the steroids tested at the maximum tolerable doses, as determined in preliminary experiments, ethinyl estradiol was the most potent promoter, inducing more hyperplastic nodules than did PB and almost 50% less gamma-glutamyl transpeptidase-positive foci. However, gamma-glutamyl transpeptidase-positive foci induced by ethinyl estradiol were twice the average size as those induced by PB. The steroids testosterone, cortisone, and dexamethasone induced more foci than did DEN alone, but few if any hyperplastic nodules. Deoxycholic acid was the most potent promoter of the bile acids tested, inducing 3 to 4 times more hyperplastic nodules than did PB and more gamma-glutamyl transpeptidase-positive foci, which were 5 times larger on the average than those induced by PB. The other bile acids tested, lithocholic acid and taurine, induced slightly more foci than did DEN alone but no hyperplastic nodules. These findings suggest that ethinyl estradiol and deoxycholic acid are relatively strong promoters of the appearance of preneoplastic lesions in hepatocarcinogenesis. (Author abstract) (22 Refs)

9. ORGAN-SPECIFIC PROMOTING EFFECTS OF PHENOBARBITAL SODIUM AND SODIUM SACCHARIN IN THE INDUCTION OF LIVER AND URINARY BLADDER TUMORS IN MALE F344 RATS.

Nakanishi K, Fukushima S, Hagiwara A, Tamano S, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizucho-cho, Mizuho-ku, Nagoya 467, Japan

JNCI; 68(3):497-500 1982

Studies were conducted to determine whether initial treatment with N-2-fluorenylacetamide (2-FAA) or N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) followed by treatment with either phenobarbital sodium (PB) or sodium saccharin (SS) induced or enhanced liver and/or bladder tumorigenesis. Male inbred F344 rats were given 0.05% PB and 5.0% SS in the diet for 32 wk after 4-wk administration of 0.02% 2-FAA or 0.01% BBN. PB significantly enhanced hepatocarcinogenesis after 2-FAA treatment and induced hyperplastic liver nodules after BBN treatment. The SS significantly enhanced induction of bladder hyperplasias, but not papilloma after BBN treatment, and induced bladder hyperplasias after 2-FAA treatment. However, PB had no effect on the bladder and SS had no effect on the liver after either 2-FAA or BBN treatment. The data indicate that although 2-FAA and BBN have tumor-initiating effects in the liver and urinary bladder, the tumor-promoting effects of PB and SS are organ-specific. The tumor-promoting effect of PB for the liver is relatively greater than that of SS for the urinary bladder. (Author abstract) (25 Refs)

10. INDUCTION OF HYPERPLASTIC LIVER NODULES IN HEPATECTOMIZED RATS TREATED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, BENZO[A]PYRENE OR PHENOBARBITAL BEFORE OR AFTER EXPOSURE TO N-2-FLUORENYLACETAMIDE.

Hasegawa R, Tatematsu M, Tsuda H, Shirai T, Hagiwara A, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Gan; 73(2):264-269 1982

The effects of pre- and post-administration of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), benzo[a]pyrene (B[a]P), and phenobarbital (PB) on the induction of hyperplastic liver nodules by N-2-fluorenylacetamide (2-FAA) were studied in F344 rats. Rats were given 3'-Me-DAB (0.06% in the diet), B[a]P (80 mg/kg b wt x 7, intragastrically) or PB (0.05% in the diet) for 6 wk before (experimental series I) or after (experimental series II) diet containing 0.02% 2-FAA for 2 wk, and killed in wk 10 of the experiment. The number and total area of hyperplastic nodules per unit area of liver were greatest in rats treated with 3'-Me-DAB in both experimental series. B[a]P significantly increased the induction of hyperplastic nodules in experimental series I and PB significantly increased it in experimental series II. Partial hepatectomy performed during administration of test chemicals enhanced the induction of hyperplastic nodules, especially in experimental series I, and an oral dose of carbon tetrachloride during 2-FAA feeding enhanced it in both experimental series. In the present system, initiating activity of both the hepato- and the non-hepatocarcinogen was detected, and promoting activity of both the hepatocarcinogen and the hepatopromoter was demonstrated. (Author abstract) (23 Refs)

11. CARCINOGENICITY AND TOXICITY OF 1,2-DIBROMOETHANE IN THE RAT.

Wong LC, Winston JM, Hong CB, Plotnick H
Res. and Development Div., Revlon Health Care Group, 1 Scarsdale Rd., Tuckahoe, NY, 10707

Toxicol Appl Pharmacol; 63(2):155-165 1982

The chronic effects of 1,2-dibromoethane (ethylene dibromide, EDB) were investigated in rats. Three experimental groups were studied: (1) inhalation of 20 ppm EDB over an 18-mo period, (2) 0.05% disulfiram (DS) in the diet for 18 mo, and (3) combined treatment of 20 ppm EDB + 0.05% DS. Rats receiving DS only showed less body wt gain than controls or EDB-exposed rats over the 18-mo period. Rats receiving EDB + DS had lower wt gain than animals receiving either EDB or DS alone. A correlation between low food consumption and low body wt gain was found in rats treated with DS or DS + EDB. EDB-treated or EDB + DS-treated rats exhibited high mortality compared with control rats or those treated with DS alone. While hematological findings were normal for EDB-treated rats, EDB + DB treatment resulted in low hematocrit, hemoglobin, and red blood cell counts. Male rats treated with DS alone did not exhibit any significant histopathological changes except for a higher incidence of hemosiderosis of the spleen; females had a higher incidence of mammary tumors and of hemosiderosis of the spleen. Rats inhaling EDB alone had a higher incidence of tumors, in one or both sexes, in the spleen, adrenal, subcutaneous mesenchymal tissue, and mammary gland compared to controls. Combined treatment with EDB + DS caused an increased incidence of tumors in one or both sexes, in the liver, kidneys, thyroid, lungs, and spleen compared to treatment with either EDB or DS alone. Combined treatment also caused a higher incidence of atrophy of the testes and spleen compared to treatment with EDB alone. These results indicate that DS, a drug used in the treatment of chronic alcoholism, enhances the toxicity and carcinogenicity of EDB. Such an effect may be significant in evaluating the hazards of industrial exposure to EDB in workers who are being treated in alcohol control programs. (37 Refs)

12. THE ANTITUMOR EFFECTS AND EFFECT ON CELL-MEDIATED IMMUNITY OF CORYNEBACTERIUM PARVUM.

Nakamura K
First Dept. Surgery, Okayama Univ. Medical Sch., Okayama, Japan

Okayama Igakkai Zasshi; 93(9/10):909-923 1981

The antitumor effects and influence on cell-mediated immunity of Corynebacterium parvum (C parvum) were studied using C3H/He mice and syngeneic mouse ascites hepatoma MH 134 tumor. With the administration of C parvum alone, a significant antitumor effect was obtained in the group given 0.4 mg per day ip for 5 consecutive days from the 5th day after transplanting 5 X 10(5) cells/0.1 ml of MH 134 tumor sc on the back. A significant antitumor effect was also obtained when C parvum was combined with MF chemotherapy (Mitomycin C 1 mg/kg, 5-Fluorouracil 25 mg/kg), in the group given MF ip on the 5th day and 0.4 mg/day of C parvum ip for 5 consecutive days from the 7th day after tumor transplantation. The cell-mediated immunity in these two groups was investigated by using the delayed type hypersensitivity (DTH) and macrophage migration inhibition factor (MIF activity). The results were: no decrease in DTH was shown compared with the tumor-bearing untreated group. MIF activity was marked compared with the tumor-bearing untreated group and tended to persist for a long period. From these findings, it was concluded that C parvum was an effective immunopotentiator which yielded an antitumor effect by restoring the cell-mediated immunity of the tumor bearing host. The effect seemed to be enhanced when used in combination with chemotherapy. (Author abstract) (47 Refs) (In JPN)

13. EFFECT OF ESTRADIOL PROPIONATE AND PREGNANCY ON CARCINOGENESIS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN C3HA MICE.

Turusov VS, Murovannyi AN, Merozova OV
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):20-23 1982

The effects of pregnancy and estradiol propionate (EP) administration on 1,2-dimethyl hydrazine (DMH)-induced carcinogenesis were studied in female C3HA mice. Virgin or pregnant females were subjected to sc administrations of DMH (8 mg/kg/wk) alone or in combination with EP (10 ug/kg/wk). DMH and EP were given for 30 wk. Animals were followed up for 50 wk after the initiation of the experiment. DMH alone induced tumors in 75% of virgin mice and in 56.2% of pregnant mice. EP administration resulted in a marked increase of the incidence of colonic tumors (31.6%, compared with 8.3% after administration of DMH alone to virgin mice and 18.7% after administration of DMH alone to pregnant mice). Uterine sarcomas were observed in 28.9% of mice treated with DMH + EP, while all mice treated with DMH alone were free of uterine sarcomas. Hepatocellular tumors were observed only in mice treated with DMH + EP (23.7%). These findings indicate that EP can modify the DMH-induced carcinogenesis not only in the hormone dependent organs but also in the liver and in the colon. (14 Refs) (In RUS)

14. QUANTITATION OF CARCINOGEN-INDUCED RESISTANCE IN RAT HEPATOCYTES TO CYTOTOXICITY BY ADRIAMYCIN IN VITRO (MEETING ABSTRACT)

Carr BI
City of Hope National Medical Center, Duarte, CA
Br J Cancer; 44(2):279 1981

The hepatocytes from rats which were treated with a variety of hepatocarcinogens in vivo have been shown to develop resistance to Adriamycin-induced cytotoxicity, as measured by an in vitro assay using trypan-blue exclusion. In order to determine the quantitative relationships between the amount of carcinogen and the subsequnt development of resistance, a single dose of 2-acetylaminofluorene (AAF) was injected into male Fischer F344 rats weighing 200-220 g and 18 h later their hepatocytes were harvested and placed in primary monolayer culture for a subsequent 24 h. Cell viability was then assessed in plates which contained Adriamycin and compared to that in controls. It was found that a single injection of 5 mg/kg AAF could induce resistance to Adriamycin (1.8 x 10-4M) when measured after 24 hr in culture. Less than 2.5 mg/kg or more than 25 mg/kg of AAF failed to induce comparable resistance. When the rats were harvested sequentially after a single dose of 5 mg/kg AAF it was found that the carcinogen-induced resistance to Adriamycin cytotoxicity was no longer present 7 days after injection. By contrast, 0.02% AAF given continuously in the diet led to a stable resistance that did not decrease with time. Resistance of Adriamycin which is induced by a single dose of carcinogen now permits the design of experiments to examine the quantitative and temporal relationships in rat liver, between induction of resistance to cytotoxicity and altered cell growth. (no Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

15. RELATIONSHIP BETWEEN CARCINOGENICITY AND IN VITRO METABOLISM OF NITROSOMETHYLETHYLAMINE, NITROSOMETHYL-N-BUTYLAMINE, AND NITROSOMETHYL(2-PHENYLETHYL)AMINE LABELED WITH DEUTERIUM IN THE METHYL AND ALPHA-METHYLENE POSITIONS.

Farrelly JG, Stewart ML, Saavedra JE, Lijinsky W
Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Cancer Res; 42(6):2105-2109 1982

With the use of rat liver preparations, the in vitro microsomal metabolism of methylethylnitrosamine, methyl-n-butylnitrosamine, and methyl(2-phenylethyl)nitrosamine labeled with deuterium in the methyl and alpha-methylene positions has been compared with that of the parent (unlabeled) compounds. All three forms of the liver carcinogen methylethylnitrosamine are metabolized with two sets of kinetic constants. Examination of these kinetic constants suggests that both methylation and ethylation of cellular nucleophiles might be important in the carcinogenic action of these nitrosamines. The esophageal carcinogen, methyl(2-phenylethyl)nitrosamine, gave only one set of kinetic constants during metabolism. The metabolism of the three methylbutylnitrosamines gave results similar to that of the three methylethyl nitrosamines. Except for metabolism of d2-methylbutylnitrosamine to butyraldehyde, two sets of kinetic constants were found. Approximately equivalent amounts of methylating species were produced from d3-methylbutylnitrosamine and d0-methylbutylnitrosamine. (Author abstract) (16 Refs)

16. 7,12-DIMETHYLBENZ[A]ANTHRACENE-DEOXYRIBONUCLEOSIDE ADDUCT FORMATION IN VIVO: EVIDENCE FOR THE FORMATION AND BINDING OF A MONOHYDROXYMETHYL-DMBA METABOLITE TO RAT LIVER DNA.

Joyce NJ, Daniel FB
(c/o Daniel) Health Effects Res. Lab., United States Environmental Protection Agency, 26 W. St. Clair St., Cincinnati, OH, 45268
Carcinogenesis; 3(3):297-301 1982

The polycyclic aromatic hydrocarbon, 7,12-dimethyl benz[a]anthracene (DMBA) is a potent carcinogen to the female Sprague-Dawley rat, and when administered under conditions that have been shown to produce cancer, results in extensive formation of hydrocarbon-deoxyribonucleoside adducts. Sephadex LH-20 and reverse-phase hplc and spectrofluorometric analysis of these adducts demonstrate that at least one adduct results from the binding of 7,12-dimethylbenz[a]anthracene-1,2,3,4-tetrahydro-3,4 dihydroxy-1,2-oxide. In these experiments, employing ip administration of the hydrocarbon, a second more polar adduct was observed. Evidence is presented that this adduct results from the formation of a monohydroxymethyl-methylbenz[a]anthracene-A-ring-diol epoxide. While both of the monohydroxymethyl-DMBA metabolites have been shown to bind cellular DNA following their administration this is the first evidence of monohydroxymethyl-DMBA-deoxyribonucleoside adducts being formed after the administration of DMBA per se. The evidence suggests that this more polar adduct is a 7-hydroxymethyl-12-

methylbenz[a]anthracene deoxyribonucleoside adduct. (Author abstract) (35 Refs)

17. THE FORMATION OF BENZO[A]PYRENE - DEOXYRIBONUCLEOSIDE ADDUCTS IN VIVO AND IN VITRO.

Ashurst SW, Cohen GM

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Carcinogenesis; 3(3):267-273 1982

The formation of DNA-bound products from benzo[a]pyrene was studied using metabolic activation systems of widely differing cellular and structural integrity. The nature of the benzo[a]pyrene-metabolite-deoxyribonucleoside adducts formed was markedly dependent on the nature of the activation system used. Systems where cellular integrity is preserved, namely mouse skin in vivo and rat liver hepatocytes and lung explants in vitro, when treated with benzo[a]pyrene, formed deoxyribonucleoside adducts of which the major one co-chromatographed with a bay-region diol epoxide-deoxyguanosine adduct, 10beta-(deoxyguanosin-N2-yl)-7beta,8alpha,9alpha trihydroxy-7,8,9, 10-tetrahydrobenzo[a]pyrene. In striking contrast, the use of activating systems with disrupted cellular integrity such as rat liver, rat lung and mouse skin microsomal fractions, in the presence of benzo[a]pyrene and exogenous DNA, resulted in the formation of deoxyribonucleoside adducts derived predominantly from either a further metabolite of 9-hydroxybenzo[a]pyrene or (+-)benzo[a]pyrene-4,5-epoxide. The consequences of such results are important when considering the widespread use of subcellular fractions such as microsomes as metabolic activating systems for short-term mutagenicity and carcinogenicity tests. (Author abstract) (41 Refs)

18. CHARACTERIZATION OF MUTAGENIC URINARY AND BILIARY METABOLITES OF THE HUMAN CARCINOGEN, BENZIDINE (BZ), IN THE RAT (MEETING ABSTRACT)

Lynn RK, Rogers RM, Garvie-Gould C, Milam DF, Scott KF, Ilias AM

Department of Pharmacology, Oregon Health Sciences University, Portland, OR, 97201

Fed Proc; 41(3):1574 1982

Bacterial mutagenicity studies of the aromatic amine BZ, suggest that the ultimate carcinogenic moiety is produced via metabolic processes. However, the chemical structure of the ultimate carcinogen(s) is currently unknown. Following iv or oral administrations of 14C-BZ, 75% of the radiolabel was excreted in the feces; approx 20% was found in the urine and 5% remained in the animal 03 days after dosing. In bile exteriorized animals up to 70% of the dose was eliminated in the bile. Urinary and biliary metabolites were separated and quantified by high pressure liquid chromatography, and the individual components characterized by mass spectrometry. N-Acetylation, hydroxylation, and glucuronidation were the major pathways leading to the formation of at least 17 radiolabeled urinary and biliary metabolites. Administration of 35S-sodium sulfate prior to BZ produced at least one BZ metabolite which contained 35S. Several of the urinary and biliary metabolites displayed significant mutagenic activity in the Salmonella typhimurium (TA98)-liver S9-beta glucuronidase assay. (no Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

19. ERADICATION OF MICROSCOPIC DEPOSITS OF LINE-10 HEPATOCARCINOMA IN THE LIVER BY ACTIVE SPECIFIC IMMUNIZATION (MEETING ABSTRACT)

Hunter JT, Sukumar S, Terata N

Laboratory of Immunobiology, National Cancer Institute, Bethesda, MD, 20205

Proc Am Assoc Cancer Res; 23:1015 1982

Guinea pigs with stage-II malignant disease were successfully treated by post-operative immunization with irradiated tumor cell vaccine. We tested the efficacy of this vaccine in eradicating line-10 cells in the organ of origin (the liver) to determine whether liver metastases were susceptible to active immunotherapy. Intraportal vein injection of line-10 cells in the strain-2 guinea pig resulted in growth of tumor foci in the liver, development of metastases in the hepatic lymph nodes and death with ascites. Growth of line-10 tumor foci could be prevented by immunization with an irradiated tumor cell vaccine containing cell wall of Mycobacterium bovis strain Bacillus Calmette-Guerin (BCG-CW) in an oil in water emulsion. Successful treatment required both line-10 tumor cells and BCG-CW emulsion; vaccines lacking either component were not effective. Immunization with irradiated line-one cells (a hepatoma antigenically distinct from line-10) did not prevent the outgrowth of line-10 cells. Active immunization was effective 1, 7 and 14 days after injection of line-10 cells. Animals rendered free of disease by vaccination rejected a challenge of line-10 cells, but not of line-one cells. This study has shown that active specific immunotherapy is an effective method for eradicating microscopic foci in the liver of a transplantable hepatocellular carcinoma. (1 Ref)

20. APPLICATION OF A MONOCLONAL ANTIBODY TO RAT HEPATOCYTES IN THE STUDY OF RAT LIVER CARCINOGENESIS (MEETING ABSTRACT)

Holmes C, Gunn B, Austin EB, Embleton MJ

University of Nottingham, Nottingham, England

Br J Cancer; 44(2):309 1981

BALB/c mice were immunized with rat hepatocytes, isolated from regenerating rat liver by perfusion and disaggregation with collagenase. Spleen cells from an immunized mouse were fused with P3NS1 mouse myeloma cells to produce hybridomas secreting antibodies to rat hepatocytes. After screening against cells derived from different rat tissues, one hybridoma was selected which produced antibody reacting preferentially with cells from regenerating and normal syngeneic liver, allogeneic liver and fetal liver. This antibody showed a borderline reactivity with normal rat kidney, but was completely negative for a range of other rat tissues and guinea-pig hepatocytes. The hybridoma was cloned, and is now producing a monoclonal antibody with identical specificity. Preliminary tests have been carried out to determine whether the expression of the antigen detected by this antibody is altered during liver carcinogenesis, and the results indicate that it is reduced or absent in some rat hepatomas. These studies are being extended to establish the stage of carcinogenesis at which this change in antigen expression occurs. (no Refs)

21. EXPRESSION OF A MONOCLONAL ANTIBODY-DEFINED LIVER-ASSOCIATED ANTIGEN IN NORMAL RAT HEPATOCYTES AND HEPATOCELLULAR CARCINOMA CELLS.

Holmes CH, Gunn B, Austin EB, Embleton MJ, Baldwin RW
Cancer Res. Campaign Lab., Univ. Nottingham, University Park, Nottingham, NG7 2RD, England
Int J Cancer; 29(5):559-565 1982

In order to examine changes in the expression of normal cellular antigens during hepatocarcinogenesis, we have developed and characterized a monoclonal antibody detecting an antigen which is particularly associated with adult rat hepatocytes. The antibody showed no reactivity with a range of freshly-prepared normal syngeneic adult rat cell types, but showed strong reactivity with hepatocytes derived from several rat strains in antibody binding tests. Immunoperoxidase staining of sections of normal rat liver showed that the antigen was distributed throughout hepatocytes within the liver, but did not stain cells other than hepatocytes. The antigen detected by this monoclonal antibody was not detectable on a number of transplanted and primary dimethylaminoazobenzene-induced hepatomas. Preliminary data indicated that this monoclonal antibody may be suitable for use in flow cytofluorimetric sorting of mixed populations of normal and tumor cells, allowing the investigation of cell phenotypes during hepatocarcinogenesis. (Author abstract) (18 Refs)

22. PATHOBIOLOGY OF HEPATITIS B VIRUS.

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Dept. Pathology, Mount Sinai Hosp. and Sch. Medicine, City Univ. New York, New York, NY, 10029
Pathobiol Annu; 11:197-228 1981

Knowledge of the pathology of hepatitis B virus (HBV) and more recent findings are discussed. The amount of virus specified unique gene products may be limited, although combined mol wt of all polypeptides from hepatitis B surface antigens (HBsAg), hepatitis B core antigen, and a cryptic form of hepatitis B antigen (HBeAg) appear to exceed the coding capacity of the small HBV genome, which is approx 100,000 daltons of protein. Recent studies indicate that HBsAg and albumin receptor activity emerge simultaneously in hepatocellular cytoplasm of HBV infected patients and also in the cytoplasm, on the cell surface, and in the supernatant culture media of an HBsAg producing hepatocellular carcinoma (HCC) cell line. The 28 nanometer core particles of HBV can be isolated from circulating Dane particles (DP) by detergent treatment or from hepatocellular nuclei of infected liver. Observation of two populations of DP may be of great biological importance since only full particles with complete genome may be infectious, whereas empty particles may be defective and interfere with replication of homologous virus. HBeAg probably is an integral structural component of the HBV nucleocapsid, coded by the genome of the virus. In serum of HBV infected patients, HBeAg occurs free or in association with IgG, most likely as immune complexes. Diseases associated with HBV infection are acute and chronic hepatitis, and a variety of clinical syndromes may be associated with HBV infection. HBV may be one of the agents involved in the etiology of human HCC. HCC in man is highly correlated with prevalence of HBsAg carriers. Serologic markers of HBV infection are found in significantly higher frequency in patients with HCC, and tumor markers are detected in HCC cells. The possibility cannot be excluded that the virus plays a merely passive role in hepatocarcinogenesis. (228 Refs)

23. HEPATITIS B VIRUS AND PRIMARY LIVER CANCER: DEMONSTRATION OF A CYTOPLASMIC TUMOR ANTIGEN IN THE TRANSFORMED HEPATOCYTE.

Romet-Lemonne JL, Barin F, Goudeau A, Maupas P
Institut de Virologie de Tours, Facultes de Medecine et de Pharmacie, 2bis, boulevard Tonnelle, 37000 Tours, France
C R Acad Sci [III] (Paris); 294(1):9-14 1982

The presence of tumor antigen was studied in human hepatoma cell line PLC/PRF/5 by indirect immunofluorescence and immunoperoxidase assay using antisera from 14 Senegalese patients with primary hepatocellular carcinomas. Ten of the 14 sera were HBs Ag-positive, 4/10 also HBe Ag-positive, 3/14 anti-HBsd antibody-positive and 1/14 anti-HBc antibody-positive. Twenty-two sera without hepatitis B virus markers from African Blood donors and from cancer patients were used as controls. Tumor antigen (HBV/T) was found in the cytoplasm of the human hepatoma cells. The same antigen was also detected in primary hepatocellular carcinoma tissues. The data obtained with serum and tissue controls indicate that the HBV/T Ag-anti-HBV/T system seems to be associated with the transformation of hepatocytes by hepatitis B virus. (15 Refs) (In FRE)

24. PRESENCE OF HEPATITIS B SURFACE ANTIGEN BEFORE PRIMARY HEPATOCELLULAR CARCINOMA.

Nomura A, Stemmermann GN, Wasnich RD
Japan-Hawaii Cancer Study, Kuakini Medical Center, 347 N Kuakini St., Honolulu, HI, 96817
JAMA; 247(16):2247-2249 1982

In a study of 7,498 men of Japanese ancestry in Hawaii, 18 incident cases of primary hepatocellular carcinoma were identified after a follow-up period of 13 yr. Sixteen of the 18 patients had stored serum specimens available for analysis. Ten of the 16 had positive serum test results for hepatitis B surface antigen in their original specimens. None of 48 matched control subjects, whose stored serum specimens were also analyzed, had similar positive test results. This finding indicates that hepatitis B surface antigenemia preceded primary hepatocellular carcinoma in many patients. (Author abstract) (20 Refs)

25. CLINICAL SIGNIFICANCE OF THE DETERMINATION OF HBSAG, ANTI-HBS AND ANTI-HBC IN VIRAL HEPATITIS AND PRIMARY LIVER CANCER.

Min X, Han Y, Wang M, Chen Z
Dept. Infectious Diseases, Nanjing Medical Coll., Nanjing, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):106 1981

Results of HBsAg, Anti-HBs and Anti-HBc determination are described for 139 cases of various types of viral hepatitis and 16 cases or primary liver cancer. There were 99 males and 56 females, 7-75 yr old. The positive rates of HBsAg, Anti-HBs and Anti-HBc in patients with viral hepatitis were 56.8%, 33.8% and 45.3%, respectively, while those in patients with liver cancer were 56.4%, 25.0%, and 62.5%, respectively. Hepatitis B was closely related to primary liver cancer. (no Refs) (In CHI)

26. CARRIER STATUS IN HEPATITIS B: A MODERN SCOURGE WITH HOPE.

Iber FL
Univ. Maryland Hosp., Batimore, MD
JAMA; 247(16):2275-2276 1982

The importance of 'carriers' of hepatitis B is discussed. The prevalence of hepatitis B surface antigen (HBsAg) carriers in the general population of the United States is estimated to be 0.2-0.5%. The majority of these patients are entirely asymptomatic, yet the carrier at times represents a clear health hazard to his contacts. The HBsAg carrier is at clear risk of liver disease and hepatocellular carcinoma (HCC). Approx 15-20% of asymptomatic carriers have significant chronic liver disease. At least one half of all patients in whom HCC develops have associated markers of hepatitis B virus. (2 Refs)

27. THE EVOLUTION, IMPLICATIONS, AND APPLICATIONS OF THE HEPATITIS B VACCINE.

Alter HJ
NIH, Bethesda, MD
JAMA; 247(16):2272-2275 1982

One aspect of hepatitis B vaccine is that it might serve indirectly as the first cancer vaccine because of the possible relationship between hepatitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC). Evidence for causality is summarized. The global distribution of hepatitis B surface antigen (HBsAg) carriers and HCC are almost identical. (14 Refs)

28. LAPAROSCOPIC EXAMINATION OF CHRONIC LIVER DISEASES: POSSIBLE RELATIONSHIP BETWEEN PATCHY MARKING AND HEPATOCELLULAR CARCINOMA.

Numa Y, Fukumoto Y, Esaki T, Oda M, Ando K, Tsubota W, Miyazaki M, Morimoto T, Matsuda S, Watanabe S, Kodama T, Okita K, Takemoto T
First Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, Yamaguchi Prefecture, Japan
Gastroenterol Endosc; 23(6):808-813 1981

The relationship between red spot patchy marker (patchy marker) and hepatocarcinoma (HCa), and between hepatitis B surface antigen (HBsAg)-hepatitis B surface antibody (HBsAb) system and morphology of lymph nodes by laparoscopic observation was investigated in 103 patients with chronic liver diseases (CLD) and 25 patients with HCa. Patchy marker was detected in 30/103 (29.1%) CLD patients: 1/15 (6.7%) with chronic non-active hepatitis, 15/50 (30%) with chronic active hepatitis, and 14/38 (36.8%) with liver cirrhosis. Twenty-three (22.3%) of 103 CLD patients had liver cell dysplasia. Of 100 CLD patients tested, HBsAg was positive in 26, and HBsAb was positive in 12. Patients without patchy marker showed a higher frequency of being positive for either HBsAg or HBsAb than those with patchy marker. In contrast, a higher value of alpha-fetoprotein was found more often in patients with patchy marker than in those without patchy marker. Of 21 HCa patients, 4 were positive for HBsAg and none for HBsAb. Patchy marker was positive in 8/21 HCa patients, 2 of whom were positive for HBsAg; patchy marker was negative in 13/21 HCa patients, 2 of whom were positive for HBsAg. These results suggest that such laparoscopic findings may be useful for identifying CLD patients at high risk for developing cancer. (16 Refs) (In JPN)

29. CYTOTOXICITY OF TUMOUR-BEARER SERUM TO D23 HEPATOMA CELLS DERIVED FROM SOLID TUMOURS, ASCITES OR IN VITRO CULTURES.

Lando P, Cabriel J, Berzins K, Perlmann P
Dept. Immunology, Univ. Stockholm, Stockholm, Sweden
Scand J Immunol; 15(3):259-266 1982

The complement-dependent cytotoxicity of antibodies in tumor-bearer serum (TBS) from rats carrying the chemically induced D23 hepatoma was investigated. Target cells were D23 cells from solid tumors (D23sol), from ascites tumors (D23asc), or from in vitro growing cell cultures (D23cc). The D23asc and D23cc cells were not lysed when used as target cells in the assay, although they evoke cytotoxic antibodies when growing in vivo. The D23 ascites cells became susceptible to complement-dependent lysis after trypsin treatment. This was, however, not due to unmasking of target antigens, since untreated D23 ascites cells absorbed cytotoxic antibodies as efficiently as trypsinized cells. No increase in susceptibility to complement-dependent lysis was observed after trypsin treatment of D23cc cells. Absorption of cytotoxic antibodies with D23cc cells showed no or very low antigen expression on the surface of these cells. They did, however, contain the antigen(s), since 3 M KCl extracts of the D23cc cells could inhibit the complement-dependent cytotoxicity of D23sol TBS against D23sol cells. From these data it was concluded that the susceptibility of hepatoma cells for antibody-mediated complement lysis is not only correlated with antigen expression, as was the case with the in-vitro-cultivated cells, but is also dependent on increased lytic susceptibility after trypsin treatment of the cells. (Author abstract) (26 Refs)

30. INFLUENCE OF THE LIVER ON THE PROFILE OF CIRCULATING ANTIGENS RECOGNIZED BY ANTISERUM AGAINST HEPATOMA MEMBRANE GLYCOPROTEINS.

Baumann H, Eldredge D
Dept. Cell and Tumor Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 42(6):2398-2406 1982

Rat hepatoma tissue culture cells have retained only a few liver-specific membrane functions. To find out whether transformation of these cells led to the appearance of tumor-specific membrane glycoprotein structures, which might also be present in released form in the circulation of tumor-bearing animals, we compared immunologically the sera and ascites fluids of normal and of hepatoma-bearing rats. For structural identification, we used polyspecific antibodies against the membrane glycoproteins of the hepatoma cells. Crossed immunoelectrophoresis of the body fluids resulted in the separation of several antigens, one of which appears to be tumor specific. Immunoelectrophorectic analyses of the glycoproteins from the membranes of liver and hepatoma cells revealed many shared antigens; in one instance, we could assign the membrane associated form to major antigen detected in the serum. Characterization of the molecular size and charge of two selected antigens by two-dimensional gel electrophoresis indicated that the hepatoma cell products were not completely sialylated. In the case of the circulating, hepatoma-specific antigen, this property appears to result in hepatic clearance of the most basic ('asialo') portion of the glycoprotein species via the receptor-mediated uptake of galactose-terminated glycoproteins. The result was the accumulation of the acidic forms of the antigen in the serum and ascites fluid of tumor-bearing rats. (Author abstract) (19 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

31. MORPHOLOGICAL AND CYTOCHEMICAL CHARACTERIZATION OF RAT HEPATOCYTES DURING CARCINOGENIC TRANSFORMATION INDUCED BY DIETHYLNITROSAMINE (DENA) (MEETING ABSTRACT)

Penasse W, Wanson JC, Bernaert D
No affiliation given
Acta Anat (Basel); 111(1/2):112 1981

Chemical hepatocarcinogenesis has been induced in adult Sprague-Dawley rats by administration of DENA at the final concentration of 70 mg/kg body weight, 24 h after partial hepatectomy. This process involves mainly three stages: preneoplastic foci already detectable 2 months after the treatment, hyperplastic nodules arising after about 9 months, and later on, hepatocarcinomas. A number of techniques were developed to study at the ultrastructural level the morphological modifications during the transformation process. Several enzymatic deficiencies affecting G6Pase and bile canalicular ATPase activities are associated with this process. These enzymatic activities constitute good markers for visualizing the evolution of the lesions and are finally the best tools for localizing these lesions by screening large surfaces of the liver making a bridge between the light microscope of the pathologist and the electron microscope of the ultrastructural knowledge. The study of this transformation with the transmission and the scanning electron microscope can be done on the cell in situ isolated by enzymatic perfusion from the liver, cultured in Petri dishes or in the whole extracted nodule. Preneoplastic hepatocytes display persistent phenotypic alterations: increase in size correlated with polyploidization, important storage of glycogen and lipids; cells frequently show an intense proliferation of the SER (smooth endoplasmic reticulum); the RER (rough endoplasmic reticulum) appears also disturbed and exhibits unusual structures. (no Refs)

32. ULTRASTRUCTURAL DIFFERENCES BETWEEN CONTROL AND NITROSOMETHYLUREA-TRANSFORMED CELLS OF RAT HEPATOCYTE ORIGIN.

Kaplan AE, Yamaguchi MK, Tralka TS, Hanna CH
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Exp Cell Res; 138(2):251-260 1982

Ultrastructural comparisons identify significant differences between a control cell, TRL 12-13, and a nitrosomethylurea-transformed cell line, NMU-3, which secretes lactic acid in vitro and produces carcinomas in vivo. Both cell lines were established from rat hepatocytes. The NMU-3 cells show a marked reduction in mitochondria, both at confluence and at 48 hr post-confluence. This deficiency supports previous biochemical findings of altered bioenergetic pathways in the NMU-3 cells, leading to increased output of lactic acid. In addition to deficiencies in mitochondria, the NMU-3 cells show a marked reduction in other membranous structures, including rough endoplasmic reticulum, Golgi apparatus, pinocytotic and coated vesicles. Polyribosome distribution at confluence and 48 hr later suggests that the transformed cells continue to synthesize intracellular protein, whereas the control cells appear to secrete protein for export at this time. (Author abstract) (29 Refs)

33. MORPHOLOGIC VARIANTS OF HEPATOCELLULAR CARCINOMA AFTER SMALL DOSES OF HEPATOCARCINOGENS IN RATS WITH REGENERATING LIVER.

Chopra P, Dhar A, Nayak NC
Dept. Pathology, All India Inst. Medical Sciences, New Delhi 110029, India
Indian J Med Res; 74:907-914 1981

Sequential evolution of hepatic neoplasms after administration of one or few small doses of dimethyl-nitrosamine and 2-acetylamino fluorene to rats with regenerating livers has been studied. A number of animals developed hepatocellular carcinoma (HCC). The commonest histologic type was a trabecular HCC. Benign biliary cystadenomas were frequent. Extramedullary hematopoiesis, vacuolation of tumor cells, fatty change and globular hyaline were often associated with HCC. Mallory's hyaline was not encountered. Tumorous and non-tumorous proliferation of Kupffer cells was a notable feature. Irrespective of the type and extent of HCC, no metastases were encountered. (Author abstract) (23 Refs)

34. INVASION OF TUMOR CELLS INTO HEPATOCYTE CULTURES: A MODEL FOR LIVER METASTASIS FORMATION (MEETING ABSTRACT)

Roos E, Middlekoop OP, Van de Pavert IV
Division of Cell Biology, The Netherlands Cancer Institute, 1066 CX Amsterdam, The Netherlands
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

We have previously described the infiltration of tumor cells into mouse liver, an important step in the formation of liver metastases. It was shown how the tumor cells interact with sinusoidal endothelial cells and hepatocytes. The latter interaction has now been investigated in cultures of isolated rat hepatocytes to which the tumor cells were added. The morphology was similar to that observed in the liver: deep invagination of the hepatocytes by the tumor cells. However, the mechanism of the interaction appeared to be different for MB 6A lymphosarcoma cells as compared to TA3 mammary carcinoma cells. This conclusion is based upon the results of morphological analysis and on the divergent effects of tubulin-binding drugs on infiltration by the two tumor cell types. Adhesion to, but not infiltration between hepatocytes of the MB 6A cells was inhibited by these drugs, whereas adhesion of the TA3 cells was not affected and infiltration actually enhanced. Using an immunological method we have obtained preliminary evidence for two different specific adhesion molecules both on hepatocytes and on MB 6A cells, involved in their interaction. High affinity of MB 6A cells for one of the hepatocyte components which is probably present exclusively at the interhepatocyte surfaces might explain the rapid infiltration of these cells between hepatocytes. (no Refs)

35. DRUG-INDUCED ALTERATIONS OF THE LIVER. HISTOLOGICAL ASPECTS.

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Acta Gastroenterol Belg; 44(9/10):367-374 1981

Histological characteristics of drug-induced liver disorders are described. Administration of methotrexate for psoriasis may result in hypertrophy and proliferation of liver fibroblasts. Liver irradiation and urethane exposure can cause obliteration of centrolobular veins. Liver adenoma, focal nodular hyperplasia, and hepatocellular carcinoma have been related to the chronic use of oral contraceptives. Exposure to vinyl chloride and ingestion of arsenic compounds has been related to the development of liver angiosarcoma. The differential diagnosis of cholestasis and other disorders, including Hodgkin's and non-Hodgkin's lymphomas is discussed. (8 Refs) (In FRE)

36. ULTRASTRUCTURAL ABNORMALITIES IN CARCINOGEN-INDUCED HEPATOCELLULAR ALTERED FOCI IDENTIFIED BY RESISTANCE TO IRON ACCUMULATION.

Hirota N, Williams GM
Dept. Pathology, Jichi Medical Sch., Minamikawachi-machi, Kawachi-gun, Tochigi-ken, Japan
Cancer Res; 42(6):2298-2309 1982

Hepatocellular altered foci were induced in rat liver by cycles of feeding of N-2-fluorenylacetamide and were distinguished by their resistance to iron accumulation following production of hepatic siderosis by dietary administration of 8-hydroxyquinoline and ferrous gluconate. The foci were readily identified by their iron exclusion in plastic-embedded sections stained for iron. Sections from iron-free regions processed for electron microscopy permitted ultrastructural study of cells in foci identified by reduced cytoplasmic ferritin. Altered foci of the eosinophilic type produced by cyclic feeding of carcinogen for 16 wk were composed of both normal-appearing hepatocytes and others with ultrastructural abnormalities, including increased agranular reticulum with associated glycogen particles, decreased rough endoplasmic reticulum with reduced length of cisternae, degranulated rough vesicles, altered and displaced Golgi complexes, and abnormal bile canaliculi. At 12 and 24 wk after cessation of carcinogen exposure, cells in persistent eosinophilic foci continued to display ultrastructural abnormalities. They possessed increased rough endoplasmic reticulum with rather regular cisternal arrangement and relatively increased smooth endoplasmic reticulum. Golgi complexes were abnormal. Bile canaliculi were abnormal and occasionally increased in number. Nuclei displayed prominent nucleoli. Cells in a basophilic focus were characterized by the presence of numerous free polyribosomes diffusely scattered throughout the cytoplasm, distended rough endoplasmic reticulum with loss of parallel-stack and hypertrophic dilated Golgi complexes, and prominent marginated nucleoli. The finding that persistent foci continued to display ultrastructural abnormalities, some of which changed or progressed in the absence of further carcinogen exposure, suggests that the persistent iron-excluding foci are a permanently altered population. (Author abstract) (56 Refs)

37. KINETICS OF PHENOTYPIC MATURATION OF REMODELING OF HYPERPLASTIC NODULES DURING LIVER CARCINOGENESIS.

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Cancer Res; 42(6):2330-2335 1982

Hyperplastic nodules appearing during the preneoplastic phase of liver carcinogenesis were divided into two types, persistent and remodeling, according to the pattern of staining for gamma-glutamyltransferase. In the resistant cell model of liver carcinogenesis used in this study, hyperplastic nodules, uniformly staining for gamma-glutamyltransferase, rapidly emerge by 4 wk after a single injection of diethylnitrosamine and brief selection by dietary 2-acetylaminofluorene plus partial hepatectomy. By 6 wk, a majority of nodules (about 75%) show an obvious irregularity and loss of uniformity in staining for gamma-glutamyltransferase while the remaining nodules continue to be uniformly stained. The number of irregularly stained nodules increases over the next 18 wk until over 95% of nodules show the nonuniform loss of enzyme activity. The progressive loss of enzyme activity is accompanied by architectural remodeling to normal-appearing liver. This is associated with the increasing disappearance of many obvious nodules from the liver as the remodeling ones blend imperceptibly with the surrounding liver. The uniformly stained nodules show the persistence of hepatocyte arrangements in plates two or more cells thick and in acini and of cytoplasmic hypertrophy characteristic of persistent hyperplastic nodules. Labeling indices are much higher in hepatocytes of the persistent uniformly stained nodules than in the remodeling ones. The possibility of exploiting this phase of the model further for in-depth analysis of the nodule-to-carcinoma sequence is discussed. (Author abstract) (39 Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

38. PRETREATMENT OF RATS WITH A SINGLE DOSE OF ACETYLAMINOFLUORENE INCREASES THE CAPACITY OF LIVER ENZYMES TO MOVE O6-METHYLGUANINE FROM DNA IN VIVO AND IN VITRO (MEETING ABSTRACT)

Cooper DP, Margison GP, O'Connor PJ
Christie Hospital, Manchester, England
Br J Cancer; 44(2):272 1981

Chronic pretreatment of rats with AAF (acetylaminofluorene) has been shown to enhance the repair of O6-methylguanine (O6-meG) and similar effects have now been obtained using single-dose pretreatments. Male Wistar rats were given AAF up to 20 mg/kg; ip 24 h before a single dose (1 mg/kg, ip) of [14C]-dimethylnitrosamine (DMN). Five h after the DMN challenge there were some variations in the amounts of 7-methylguanine (7-meG) and 3-methyladenine (3-meA) in the liver DNA of control and pretreated groups. However, the 3-meA/7-meG ratio was similar in all cases, while the O6-/7-meG ratio was reduced after 20 mg AAF/kg, suggesting that repair of O6-meG was enhanced. The effect was not specific for DMN-induced damage, as the repair of O6-meG produced in liver by MNU was also enhanced. Incubation of cell-free liver extracts with MNU-methylated DNA in vitro decreased the amount of O6-meG in the acid precipitable DNA. This decrease was protein-dependent, but no free O6-meG base was found in the acid supernatants. Extracts from control rats destroyed 21% of the O6-meG in the substrate, while extracts from animals pretreated with 6.67, 20 or 60 mg AAF/kg destroyed 40, 77 and 90% of the O6-meG respectively. The effects observed in vivo were therefore probably due to an increased production of repair enzyme. AAF pretreatment did not affect 7-meG glycosylase activity in cell-free extracts. There was a 20-fold increase in the incorporation of [3H]-dT into hepatic DNA of rats pretreated with 20 mg AAF/kg, while lower doses had no effect. The enhancement of O6-meG repair could therefore be related either to cell proliferation as a result of the hepatotoxicity of AAF or to the induction of repair enzymes in response to sublethal DNA damage. (1 Ref)

39. LIVER DNA BOUND IN VIVO WITH AFLATOXIN B1 AS A MEASURE OF HEPATOCARCINOMA INITIATION IN RAINBOW TROUT.

Whitham M, Nixon JE, Sinnhuber RO
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JNCI; 68(4):623-628 1982

The in vivo binding of aflatoxin B1 (AFB1) to liver DNA was measured in rainbow trout subjected to various regimens and in coho salmon to determine if binding would correlate with tumor incidence and initiation of hepatocellular carcinoma. Establishment of time-course binding parameters showed no significant difference between 4, 12, 24, or 48 hr. Doses of 5, 25, 100, and 300 ug AFB1/kg body wt produced an almost linear increase in binding with increasing dose. Compared to that of controls, AFB1-DNA binding was 2-fold lower in beta-naphthoflavone-treated trout and 20-fold lower in coho salmon. These two comparisons reflected a decrease in the effective activation and binding of AFB1, correlated with tumor incidence, and are believed to correlate with a decrease in the initiation of hepatocellular carcinoma. AFB1 binding was not significantly altered by dietary protein or cyclopropenoid fatty acids, which are thought to increase hepatocellular carcinoma incidence through promotional effects. The data were consistent with the view that in vivo binding of AFB1 to liver DNA is a measure of cancer initiation by AFB1 and correlated with the incidence of hepatocellular carcinoma in salmonid fish. (Author abstract) (52 Refs)

40. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTES FOLLOWING IN VIVO TREATMENT WITH DINITROTOLUENE.

Mirsalis JC, Butterworth BE
SRI International, Building 205, 333 Ravenswood Ave., Menlo Park, CA, 94025
Carcinogenesis; 3(3):241-245 1982

The purpose of this study was to examine the induction of unscheduled DNA synthesis (UDS) by the potent hepatocarcinogen technical grade dinitrotoluene (tgDNT; 76% 2,4-dinitrotolulene, 19% 2,6-dinitrotolulene) using the in vivo-in vitro hepatocyte DNA repair assay. Male Fischer-344 rats were treated by gavage and hepatocytes were isolated by liver perfusion and cultured with [3H]thymidine. UDS was measured by quantitative autoradiography as net grains/nucleus (NG); greater than or equal to NG was considered positive. Controls consistently had-3 to-6 NG. A dose-related increase in UDS was observed 12 hr after treatment, with 200 mg/kg tgDNT producing 26 NG. A 50-fold increase in the number of cells in S-phase was observed at 48 hr after treatment. This increase in S-phase cells could be suppressed in the presence of 10-20 mM hydroxyurea (HU), while the same levels of HU did not affect the level of UDS at 12 hr after treatment. 2,4-DNT produced only a weak response, in contrast to 2,6-DNT which was a potent inducer of UDS. Treatment of female rats with tgDNT yielded only modest increases in UDS and DNA replication relative to males. These results are consistent with the carcinogenicity studies and indicate that tgDNT is a potent genotoxic agent, with 2,6-DNT contributing the major portion of the effect. (Author abstract) (20 Refs)

41. EFFECT OF AFLATOXIN B1 ON THE REPAIR OF O6-METHYLGUANINE IN THE HEPATIC DNA OF RATS AND MICE (MEETING ABSTRACT)

Maru GB, Margison GP, Chu YH, O'Connor PJ
Christie Hospital, Manchester, England
Br J Cancer; 44(2):273 1981

Pretreatment of male Wistar rats by ip injection of single (2 mg/kg) or multiple (4x0.5 mg/kg) doses of aflatoxin B1 (AFB) stimulates the process for the removal of O6-methylguanine from hepatic DNA in animals challenged with a single dose (2 mg/kg) of [14C]-dimethylnitrosamine (DMN). The sensitivity of this system in terms of its ability to 'adapt', is indicated by the fact that the repair response can be detected as early as one day after pretreatment with a single dose. However, treatment of mice (C57Bl, males) with doses from 0.1 to 100 mg/kg of AFB, had no marked effect on the activity of the O6-meG repair system, when assayed in vitro using cell-free liver extracts and DNA methylated with [3H]-MNU as substrate. This murine repair system has been titrated in vivo, using a range of doses of [14C]-DMN (0.25-10 mg/kg). In terms of saturation kinetics it appears to be intermediate between the Syrian golden hamster and the rat but more closely resembling that for the rat. Different doses of AFB and exposure periods are under investigation, but it is tentatively concluded that the mouse, like the hamster and in contrast to the rat, is refractory to the inducibility of the O6-meG repair system. (3 Refs)

42. ALTERATIONS IN DNA-DEPENDENT RNA POLYMERASE I FROM RAT LIVER ACCOMPANYING ETHIONINE ADMINISTRATION.

Yamano H, Sawai Y, Thung WL, Sato F, Tsukada K
Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Biochem Biophys Res Commun; 105(3):799-805 1982

Repeated administration of ethionine, an hepatocarcinogen and the ethyl analogue of the amino acid methionine, was found to increase the activity of RNA polymerase I from rat liver nuclei 3-to 4-fold when given simultaneously with adenine. It is suggested that changes in RNA polymerase I levels observed after ethionine administration may constitute an important early biochemical event in the liver that triggers cellular proliferation leading to the development of neoplasia. (27 Refs)

43. PLASMA MEMBRANE CHANGES OF LIVER AND MORRIS HEPATOMA INDUCED BY RETINOL IN RATS.

Buchsel R, Reutter W
Medizinische Klinik der Albert-Ludwigs-Universitat, Hugstetter Strasse 55, D-7800 Freiburg, W. Germany
Cancer Res; 42(6):2450-2456 1982

The uptake and binding of po-administered labeled all-trans-retinol was studied in vivo in rats bearing nine different types of Morris hepatomas. Radioactivity was found in acid-precipitable and acid-soluble fractions of serum, liver, and the respective tumor. In the different types of Morris hepatomas, the uptake of retinol was found to be decreased. Evidently, the decreased uptake of retinol is a common feature of Morris hepatomas and seems to be related to malignant transformation and not to increased growth. A 67% decrease in the incorporation rate of labeled L-fucose and a simultaneously increased turnover of protein-bound L-fucose were the major alterations of the fucoprotein metabolism in the plasma membrane fraction of the liver induced by high doses of retinol. Protein synthesis in

retinol-treated rats was unchanged in liver, hepatoma and serum protein during the 1st hr after pulse. However, 2 hr after the L-methionine pulse, an additional increase of the incorporation rate was observed. Fluorographic analysis of the plasma membrane polypeptides revealed characteristic changes in the labeling pattern after labeling with L-fucose in vivo. This study indicates that the increased hepatic secretory activity after high doses of retinol leads to rapid turnover of incompletely fucosylated glycoproteins of the plasma membrane. The subsequent alterations in the glycosylation pattern as revealed by labeling with L-fucose in vivo are not detectable in the tumor plasma membrane. Therefore, the tumor plasma membrane is not the main target organelle of retinol. Possibly, changes in the host rather than in the tumor itself may be responsible for the anticarcinogenic effect of retinol and the retinoids. (72 Refs)

44. POLYAMINE METABOLISM IN MALIGNANT TUMORS.

Siatkin SP, Berezov TT
P. Lumumba Univ. People's Friendship, Moscow, USSR
Vestn Akad Med Nauk SSSR; (3):10-21 1982

The metabolism of polyamines (PA) was studied in random-bred albino rats with hepatoma 27 induced by diethylnitrosamine and in C3HA mice with hepatomas 22a, 61, 60, 48, and 46 induced by o-aminoazotoluene. PA content in hepatoma tissue was significantly greater than that in the normal liver. In all hepatomas except hepatoma 22a. The rate of ornithine carboxylation was significantly greater than that in the normal liver. All hepatomas were characterized by a virtual absence of diamine oxidase (DAO) activity. Significant increase of PA content and the increase of ornithine decarboxylase activity were observed 4-5 mo after the initiation of carcinogen administration, while the decrease of DAO activity was observed 1.5-3 mo after the initiation of the experiment. These findings indicate that the changes in the rate of PA oxidation can be considered as the primary manifestations of hepatocarcinogenesis, while the changes in ornithine decarboxylation reflect the tumor progression or dedifferentiation of tumor cells. (56 Refs) (In RUS)

45. ACUTE EFFECTS OF DIEMTHYLNITROSAMINE (DMN) ON COMPOSITION AND SYNTHESIS OF RAT LIVER CHROMATIN PROTEINS (MEETING ABSTRACT)

Huang PH, Magee PN, Stewart BW
Temple University School of Medicine, Philadelphia, PA, 19140
Fed Proc; 41(3):687 1982

Administration to rats of the potent hepatocarcinogen DMN is followed by the methylation of hepatic nucleic acids and proteins. Consequent secondary structural changes in DNA may be detected by column chromatography on benzoylated DEAE (diethylaminoethyl)-cellulose. As part of the further investigation of nitrosamine-induced injury, short-term alterations in the composition of rat liver chromatin proteins have been analyzed. Administration of DMN (10 mg/kg) was associated with a proportional increase in the recovery of rat liver chromatin proteins for at least 48 hr after treatment and a biphasic increase in the incorporation of 14C-leucine into chromatin proteins. Upon further analysis of these proteins by one- and two-dimensional gel electrophoresis, changes in the histones and non-histone proteins electrophoretic mobility and staining intensity were detected. Incorporated 14C-leucine was distributed throughout all chromatin protein fractions analyzed 4 hr after DMN. During the period 24-48 hr, apparent preferential incorporation into histones occurred while at later times non-histone proteins were more highly radioactive. (no Refs)

46. CHANGES IN HEPATIC NONHISTONE CHROMOSOMAL PROTEINS (NHCP) DURING CARCINOGENESIS INDUCED BY DIVERSE CARCINOGENS (MEETING ABSTRACT)

Ramagli LS, Lee J, Becker FF, Rodriguez LV
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):1176 1982

The NHCP of purified chromatins of normal, regenerating rat liver, stages in acetylaminofluorene (AAF) and diethylnitrosamine (DEN) carcinogenesis and resulting primary hepatocellular carcinomas (PHC) were analyzed by 2-dimensional polyacrylamide gel electrophoresis to detect changes in gene-controlling-proteins common to malignant evolution by diverse carcinogens. The NHCP were extracted with 3 M NaCl-7 M urea in Tris buffers containing phenylmethylsulfonylfluoride (PMSF), nucleic acids removed by ultracentrifugation, proteins recovered after dialysis by lyophilization and analyzed by 2-dimensional polyacrylamide electrophoresis and silver staining. A 7% qualitative difference in resolved NHCP was observed in AAF and DEN tissues but only 28% of these were in common. Approximately half of the changes detected in AAF and DEN treated tissues were found to reflect cell proliferative state, and, therefore, probably not correlated with malignant conversion. Of the new proteins detected, none exhibited a molecular weight (MW) greater than 62,000 daltons (d). In addition to the appearance of new proteins, AAF and DEN, chromatins exhibited selective losses of proteins found in normal chromatins. These results indicate that while AAF and DEN produce a number of changes in NHCP unique to each carcinogen, only 6% are common and analysis of these might serve as logical starting points for continued studies. (no Refs)

47. PROTEIN COMPOSITION OF LIVER ENDOPLASMATIC RETICULUM IN NORMAL RATS AND IN RATS EXPOSED TO CARCINOGEN N-DIETHYLNITROSAMINE.

Berdinskikh NK, Mel'nikova NN, Livshits VI
R. E. Kavetskii Inst. Problem Oncology, Kiev, USSR
Vestn Akad Med Nauk SSSR; (3):48-52 1982

The changes of the protein composition of liver endoplasmatic reticulum (ER) were studied in random-bred albino rats exposed to N-diethylnitrosamine (DENA). Electrophoretic spectrum of ER proteins during DENA-induced hepatocarcinogenesis did not differ from that in normal liver. Analysis of protein composition of separated ribosomes showed decrease of the content of the fraction with mol wt of 50,000 daltons and increase of the content of fractions with mol wt of 150,000 and 170,000 daltons. The changes in the content of these three protein fractions were associated with the stages of DENA-induced hepatocarcinogenesis. (22 Refs) (In RUS)

48. ALTERATIONS OF BIOELECTRIC POTENTIAL IN PRIMARY HEPATOCELLULAR CARCINOMAS INDUCED BY N-2-FLUORENYLACETAMIDE OR DIETHYLNITROSAMINE.

Lai CN, Becker FF
(c/o Becker) Section Experimental Pathology, Dept. Pathology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. Houston, Houston, TX, 77030
Cancer Biochem Biophys; 6(1):1-6 1982

Primary hepatocellular carcinoma(s) induced in rats by N-2-fluorenylacetamide (AAF) or diethylnitrosamine (DEN) were examined for their bioelectric potential (EP). N-2-Fluorenylacetamide-induced PHC differed from age-matched normal livers by a mean of-12.9, which is significant at p less than 0.001. They also differed from non-PHC-bearing surrounding liver by-4.75 mV, significant at p less than 0.05. Diethylnitrosamine-induced PHC differed from normal liver by-13.5 mV and from background liver by-9.95 mV, both significant at p less than 0.001. To determine the contribution of cell division to these differences, regenerating livers were examined. The levels of mixed function oxidases in PHC and in regenerating livers reported in the literature appeared to correlate with the measured EP. We, therefore, studied the effects of chemical inhibitors and an inducer of this enzyme system. The alterations of mixed function oxidase were demonstrated to parallel those of EP. (Author abstract) (35 Refs)

49. LIPID COMPONENT OF MEMBRANES OF ENDOPLASMATIC RETICULUM OF RAT LIVER DURING CARCINOGENESIS INDUCED BY DIETHYLNITROSAMINE.

Berdinskikh NK, Sanina KL, Gula EP, Mel'nikova NN
R. E. Kavetskii Inst. Problem Oncology, Kiev, USSR
Vestn Akad Med Nauk SSSR; (3):53-57 1982

The effect of diethylnitrosamine (DENA) hepatocarcinogenesis on the phospholipid (PL) and cholesterol content in the liver endoplasmatic reticulum was studied in random-bred albino rats. The most pronounced increase of PL content was observed during the 1st and 20th wk of carcinogenesis. The increase of cholesterol content was detected only during the late stage of carcinogenesis. (14 Refs) (In RUS)

50. CHANGES IN ACTIVITIES OF URIDINE DIPHOSPHATE-GLUCURONYL-TRANSFERASES DURING CHEMICAL HEPATOCARCINOGENESIS.

Yin Z, Sato K, Tsuda H, Ito N
(c/o Sato) Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, 5, Zaifu-cho, Hirosaki 036, Japan
Gan; 73(2):239-248 1982

Changes in the activities of hepatic uridine diphosphate-glucuronyltransferases (UDP-GTs) were investigated during the induction of hyperplastic nodules (enzyme-altered foci) by a system consisting of diethylnitrosamine (DEN) followed by N-2-fluorenylacetamide (FAA) and including partial hepatectomy. The activity of the late fetal form of UDP-GT, which was assayed towards o-aminophenol (o-GT activity), was induced rapidly by a single ip injection of DEN (200 mg/kg) or 3-methylcholanthrene (40 mg/kg) or by the continuous administration of FAA (0.02% in diet) alone. The activity further increased with the appearance of the nodules, while the activity of the neonatal form, which was assayed toward phenolphthalein (p-GT activity) and was inducible by phenobarbital, increased only slightly. The increased o-GT activity showed a good correlation with the increased number or area of enzyme-altered foci detected by gamma-glutamyltransferase activity staining, but the p-GT activity did not, though it was significantly increased. In hyperplastic nodules and well differentiated hepatomas induced by DEN (0.1% in drinking water, 3 wk) but isolated long after cessation of DEN, o-GT activity was markedly increased, but p-GT activity was decreased or remained at the level of normal rat liver. These data indicate that the increased o-GT activity may be one of the enzyme markers for preneoplastic hepatic cells. An antioxidant, butylated hydroxyanisole (BHA) (0.75% in diet), markedly elevated the hepatic o-GT activity rapidly after being administered with FAA in the above system, and the induction of the nodules was inhibited. (Author abstract) (32 Refs)

51. HEPATIC LEVELS OF S-ADENOSYLETHIONINE AND S-ADENOSYLMETHIONINE IN RATS AND HAMSTERS DURING SUBCHRONIC FEEDING OF DL-ETHIONINE.

Hyde CL, Poirier LA
(c/o Poirier) Nutrition and Metabolism Section, Lab. Comparative Carcinogenesis, NCI/Frederick Cancer Res. Facility, Building 538, Room 205, Frederick, MD, 21701
Carcinogenesis; 3(3):309-312 1982

The levels of S-adenosylethionine (AdoEt) and of S-adenosylmethionine (AdoMet) in the livers of weanling male rats and male and female hamsters fed ethionine for 1-6 wk were determined. In both species the hepatic contents of AdoEt were dependent upon the level of ethionine in the diet. For the 6-wk experimental period the hepatic levels of AdoEt averaged 81 ug/g liver in male hamsters fed 0.1% ethionine in the diet and 160 ug/g in those fed 0.3% ethionine; the corresponding AdoEt levels in female hamsters were 104 and 191 ug/g liver, respectively. No marked shifts in hepatic AdoEt levels were seen in either male or female hamsters although a gradual rise in hepatic AdoEt from 145 to 233 ug/g was noted in the female hamsters receiving 0.3% ethionine in the diet for 1-6 wk. AdoEt levels in the livers of rats fed 0.3% ethionine were quite variable. In rats fed the 0.1% ethionine diet the liver AdoEt levels dropped from 103 to 61 ug/g from wk 1 to 6. In animals fed the ethionine-free diet, the hepatic contents of AdoMet were relatively constant throughout the 6-wk experimental period. Chronic ethionine administration always suppressed hepatic AdoMet levels. This suppression was generally greater in animals fed the 0.1% ethionine than in those fed the 0.3% ethionine diet. Thus, the av hepatic AdoMet levels in rats, male hamsters and female hamsters receiving the 0.1% ethionine diet for 3-6 wk were 32, 18, and 45% respectively, of the corresponding AdoMet levels in animals receiving the 0.3% ethionine diet were 66, 42, and 62% of the respective control values. Feeding 0.1% ethionine to male hamsters led to exceedingly low levels of liver AdoMet (1.4-2.9 ug/g). No direct correlations could be made between the effects of ethionine feeding on the hepatic AdoEt and AdoMet levels in rats and hamsters and the previously reported differences in carcinogenicity by ethionine in these species. (26 Refs)

52. TRANSFORMATION BY ETHIONINE AND S-ADENOSYLETHIONINE OF RAT LIVER EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT)

Wilson MJ, Brown JD, Poirier LA
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Fed Proc; 41(3):281 1982

A normal line of rat liver epithelial cells was grown in Williams' Medium D in the presence and absence of the hepatocarcinogen DL-ethionine. The treated cells were exposed for 12 weeks to 2 levels of ethionine, 5.0 and 7.5 mM. The cultures were then maintained in carcinogen-free medium for an additional 31 weeks. At 4 week intervals throughout the experiment the cells were tested for transformation by: 1) carcinoma production following subcutaneous injection of cells into syngeneic hosts and 2) growth in soft agar. Twenty-one weeks after cessation of treatment, growth in soft agar was observed in cultures treated with both levels of ethionine, and tumors were produced in animals injected of ethionine, and tumors were produced in animals injected with cells treated with 7.5 mM ethionine. Control cultures remained untransformed throughout the experiment. The experiment was repeated using medium in which methionine was replaced by homocysteine. Ethionine was more toxic under these growth conditions;

therefore, levels of 0.2 and 0.375 mM L-ethionine were used. In the same study cells were also treated with 0.065 and 0.2 mM L-S-adenosylethionine. Both compounds resulted in transformation of the hepatocytes 8 weeks after cessation of treatment. The results indicate that ethionine transforms hepatocytes in culture and that S-adenosylethionine may be a proximal carcinogenic metabolite of ethionine. (no Refs)

53. THE ASSAY OF MICROSOMAL EPOXIDE HYDROLASE IN NORMAL AND PATHOLOGICAL HUMAN LIVER.

Craven AC, Walker CH, Murray-Lyon IM
(c/o Walker) Dept. Physiology and Biochemistry, Univ. Reading, Reading, England
Biochem Pharmacol; 31(7):1321-1324 1982

Samples of normal and pathological human liver were assayed for microsomal epoxide hydrolase activity using the chlorinated epoxide HEOM as substrate. The enzyme activity in liver samples from normal patients was 72.3 +-9.8 nmoles mg protein/min which is comparable to the highest values recorded in mammals, and much higher than those found in rats and mice. A microassay procedure was developed to enable the estimation of activity in needle biopsy samples (5-20 mg), obtained from patients with normal and diseased livers. Three epileptic patients who had received regular doses of phenobarbitone and/or phenytoin showed activities significantly higher than those found in all other samples (P less than 0.01). These appeared to be examples of enzyme induction. Assays were also performed on samples from six patients with alcohol-related liver disease and one patient with hepatocellular carcinoma. The role of epoxide hydrolase in the metabolism of carcinogenic epoxides is discussed in relation to these findings. (Author abstract) (18 Refs)

54. IN VIVO INACTIVATION BY ACIVICIN OF CARBAMOYL-PHOSPHATE SYNTHETASE II IN RAT HEPATOMA.

Aoki T, Sebolt J, Weber G
(c/o Weber) Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianpolis, IN, 46223
Biochem Pharmacol; 31(6):927-932 1982

The antitumor drug acivicin, L-(alphaS,5S)-alpha-amino-3-chloro-4,5-dihydro-5 isoxazoleacetic acid, in vivo irreversibly inactivated carbamoyl-phosphate synthetase II (glutamine-dependent; EC 6.3.5.5), the first and rate-limiting enzyme of de novo pyrimidine nucleotide biosynthesis, in transplantable rat hepatoma and host liver. With two injections of 0.5 mg acivicin per 100 g body wt to one group and two injections of 5 mg to another group, enzyme activity decreased to 20 and 1% in hepatoma and to 99 and 31% in liver, respectively. Aspartate carbamoyltransferase (EC 2.1.3.2) activity was not affected. Acivicin in vitro selectively inactivated glutamine-dependent activity of the synthetase II from the hepatoma and liver, with an inactivation constant (Kinact) of 90 uM and a min inactivation halftime (T) of 0.7 min. The inactivation velocity with 10 uM acivicin was 5.0-fold stimulated by 2 mM MgATP and 18.4-fold by 2 mM MgATP plus 16.7 mM bicarbonate. MgATP at 0.5 mM caused half-max stimulation of the inactivation velocity. Under in vitro conditions, L-glutamine (1 mM) protected the enzyme from inactivation by 10 uM acivicin. The synthetase activity was protected in vitro by 6 mM concentrations of glycine (84%), L-glutamate (59%) and L-aspartate (51%) and by 0.5 mM UTP (35%) from inactivation by 20 uM acivicin. The results are compatible with the suggestion that acivicin is an active site-directed affinity analog of L-glutamine. (Author abstract) (23 Refs)

55. DISTRIBUTION OF THE LIVER CARCINOGEN METHAPYRILENE IN FISCHER RATS AND ITS INTERACTION WITH MACROMOLECULES.

Lijinsky W, Muschik GM

Chemical Carcinogenesis Program, Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701

J Cancer Res Clin Oncol; 103(1):69-73 1982

The anti-histaminic drug methapyrilene hydrochloride, which induces liver tumors in rats, was labeled with tritium by exchange and administered at a dose of 21 mg containing 700 uCi to each of 15 male Fischer rats. At 1 h, 6 h, 14 h, 24 h, and 44 h after treatment three rats were killed and their livers, pancreas, kidneys, and lungs were removed. The pooled organs were homogenized and DNA, RNA, and soluble protein were isolated from each. The extent of interaction of radioactive methapyrilene with liver nucleic acids was exceedingly small and did not differ significantly from the binding to nucleic acids in kidney, lung, or pancreas, which are not target organs of this carcinogen in rats. Binding of radioactivity to soluble proteins of the liver was considerable and substantially greater than in the other organs. If the mechanisms of carcinogenic action of methapyrilene involves covalent interaction with DNA this must be at a very low and highly specific level. (Author abstract) (4 Refs)

REVIEWS AND OTHER RELATED STUDIES

56. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?

Weinhouse S

Fels Res. Inst., Temple Univ. Sch. Medicine, Health Sciences Center, Philadelphia, PA, 19140

JNCI; 68(3):343-349 1982

Roles of isozymes in cancer, examples of isozyme alteration in hepatomas, fetal isozyme expression in hepatomas, tumor-associated proteins, ectopic isozymes, loss of adult liver enzymes, and significance of isozyme alterations are reviewed. Striking changes in properties of serum aldolase in several human diseases have been observed. The serum enzyme resembled that of muscle aldolase in some muscular diseases and resembled that of liver aldolase in hepatitis or liver glycogen storage disease. In liver tumor patients the serum had the muscle isozyme. As with aldolase B, glucokinase is lost to varying degrees in hepatomas, depending on the growth rate and degree of dedifferentiation, and is replaced completely in fast-growing, poorly differentiated hepatomas by one or more of the other three hexokinase isozymes that are present in fetal liver. At least three distinct genotypic forms of alkaline phosphatase are present in human tumors and in plasma of cancer patients. An example of the resurgence of a fetal isozyme in tumors is gamma-glutamyl-transpeptidase. This enzyme is bound to the plasma membrane and is normally low in adult rat liver but very high in fetal liver and chemically induced hepatomas. Studies in which pyruvate kinase (PK) was specifically inhibited in Ehrlich ascites cells provide further suggestive evidence that the replacement of a tightly controlled hepatic PK by a high activity of the fetal form may be responsible for the high glycolytic activity of rapidly growing, poorly differentiated hepatomas. (57 Refs)

57. PRENEOPLASTIC RAT LIVER NODULES CONTAIN ONLY ONE OF THE TWO FORMS OF NORMAL LIVER MICROSOMAL EPOXIDE HYDROLASE (MEETING ABSTRACT)

Griffin MJ, Vaz AD, Kizer DE, Thomas PE, Griesmann GF
Department of Biochemistry, University of Oklahoma Health Science Center, Oklahoma City, OK, 73104
Fed Proc; 41(3):917 1982

We have confirmed the report of several other groups who found two forms of normal rat liver microsomal epoxide hydrolase which were immunologically similar (double-diffusion line of identity), but could be separated on carboxymethyl (cm) cellulose at pH 6.5. The slightly acidic (A form) is not retained on the column and appears to have a stoichiometric amount of an acid 14K polypeptide associated with the hydrolase catalytic subunit (50K), while the slightly basic (B form) has only a 50K subunit as shown by amino acid analysis and analytical SDS/PAGE (sodium dodecyl sulfate/polyacrylamide gel electrophoresis). The purified A form has 22-30% of the styrene oxide hydrolase activity of the purified B form. Male Sprague-Dawley rats fed 0.05% 2-acetylaminofluorene for 3-4 mo develop liver nodules, presumptive precursors of hepatomas. Nodule hydrolase is induced, and has been shown to be released from incubated microsomes by endogenous proteolytic activity. All solubilized nodule microsomal hydrolase is retained on CM cellulose, pH 6.5, indicating the absence of binding of the 14K acidic polypeptide. The absence of the acidic polypeptide from nodule microsomal hydrolase may decrease membrane amphiphilic interactions of A with B allowing proteolysis to occur. (no Refs)

58. PATTERNS OF HEPATOCYTE INJURY IN MAN.

Sherlock S
Dept. Medicine, Royal Free Hosp. Sch. Medicine, Pond St., London NW3 2QG, England
Lancet; 1(8275):782-786 1982

Three patterns of hepatocyte injury in man (direct, immunological, and cholestatic) are described. The characteristics of the direct pattern are predominantly mitochondrial damage, central (zone 3) necrosis, and, usually, fatty change. It can be subdivided into the alcohol type (also seen with obesity, in diabetes, as a reaction to perhexiline, in Wilson's disease, and in Indian childhood cirrhosis) and the Reye's syndrome type (also seen with tetracycline toxicity, fatty liver of pregnancy, and cytotoxic drugs). Reactive drug metabolites, metal poisoning, and anoxia are also associated with the direct pattern of hepatocyte injury. The immunological pattern is characterized by damage to cell membranes with piecemeal necrosis of periportal (zone 1) hepatocytes and mononuclear-cell infiltration. Examples include chronic active hepatitis, primary biliary cirrhosis, and drug reactions such as those to halothane. In the cholestatic pattern there is disturbance of the bile-secretory mechanism with retention of bile within the hepatocytes. Cholestatic liver injury may be intrahepatic, as in sex-hormone cholestasis, or extrahepatic, as in choledocholithisasis or carcinoma of the bile ducts. Identification of the type of hepatocyte injury is valuable in diagnosis, in assessing prognosis, and in selecting treatment. (Author abstract) (45 Refs)

59. INHIBITION BY THE LANDSCHUTZ ASCITES CARCINOMA OF THE GRANULOMATOUS INFLAMMATORY RESPONSE TO C. PARVUM.

McIntosh LC, Pugh-Humphreys RG, Fraser RA, Thomson AW
(c/o Thomson) Kolling Inst. Medical Res., Royal North Shore Hosp. Sydney, St. Leonards, N.S.W. 2065, Australia
Br J Cancer; 45(4):598-612 1982

Ip or iv administration of Corynebacterium parvum (CP) to MF1 mice induces a generalized inflammatory response, associated with marked hepatosplenomegaly and accompanied by a pronounced granulomatous response in the liver. Injection of the Landschutz ascites carcinoma (LAC) 24 hr after CP substantially reduced the intensity of the inflammatory response, and decreased both the frequency and size of the hepatic granulomas, as revealed by morphometric analysis of histological sections. The difference in cellular composition of the granulomas between the experimental groups, as revealed by light microscopy, was further emphasized and characterized by ultrastructural studies. These revealed the predominance of macrophages within the granulomas in tumor-bearing mice, in contrast to the predominance of epithelioid cells in the lesions which developed in mice given CP alone. Our experimental findings show that the inhibitory effect of the growing LAC on granuloma formation in response to CP cannot be ascribed to (a) sequestration of the microorganism within the growing tumor, (b) a nonspecific inflammatory stimulus, (c) diversion and sequestration of mononuclear phagocytes in the growing tumor or (d) the presence of lactate dehydrogenase-elevating virus in either the host or tumor cells. The inhibition of liver granuloma formation is consistent with an effect mediated by soluble, heat-stable tumor-associated factor(s). (Author abstract) (59 Refs)

60. CURRENT STATUS OF CLINICAL INVESTIGATION ON HEPATITIS, LIVER CIRRHOSIS AND HEPATIC CARCINOMA IN CHINA.

Lin Z
Zhongshan Hosp., Shanghai First Medical Coll., Shanghai, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):79-81 1981

Recent progress in the etiology, diagnostic techniques and treatments is reviewed for hepatitis, liver cirrhosis and liver cancer. The roles of hepatitis B virus, hepatitis B surface antigen, alpha-fetoproteins and numerous enzymes useful in diagnosis are specially discussed. Other topics covered include new diagnostic instrumentation, such as B-mode ultrasonography, scintigraphy, computed tomography and fiber optics. (no Refs) (In CHI)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

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Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
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EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. HEPATOCELLULAR CARCINOMA IN AN URBANISED BLACK COMMUNITY. A CHANGING PATTERN.

Paterson AC, Isaacson C
Dept. Pathology, Baragwanath Hosp., Sch. Pathology South African Inst. Medical Res., Johannesburg 2000, South Africa
Virchows Arch [Pathol Anat]; 395(3):273-278 1982

Hepatocellular carcinoma has been extensively studied in Southern Africa, and particularly its relationship to hepatitis B virus infection. Most of this work involved rural black populations. In this study the impact of urbanization on this relationship is investigated. The material is derived from the laboratory records at Baragwanath Hospital which serves the Black urban community of Soweto. Cases autopsied during the periods 1956-1960 and 1976-1980 have been examined with regard to age, sex, underlying cirrhosis and presence of HBsAg in the non-tumor liver. In addition, all biopsies from 1955 to 1980 have been analyzed with respect to age and sex. There is evidence of a significant increase in overall av age and in the pro-

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portion of female cases, while the percentage of HBsAg positive cases has fallen. Possible causes for these findings are considered. (Author abstract) (34 Refs)

2. HEPATOCELLULAR CANCER IN SWEDEN: INCIDENCE 1961-1962 AND 1971-1972.

Axelsson G
Dept. Environmental Hygiene, Univ. Gothenburg, Box 33031, S-400 33 Gothenburg, Sweden
J Chronic Dis; 35(6):459-466 1982

The present study was undertaken to compare the incidence of hepatocellular cancer in Sweden during 1961-1962 and 1971-1972, and to evaluate the geographical distribution of the disease. Another aim was to determine whether a retrospective analysis of hospital records of individual cases could provide information on relevant risk factors, in particular cirrhosis, previous diseases, occupational exposure and alcohol consumption. The incidence of hepatocellular cancer in Sweden has increased, particularly in the highest age groups. A difference in incidence for males between the three largest cities in Sweden and the remainder of the country is demonstrated. The proportion of autopsies in Sweden, particularly in the highest age groups, has increased between the two time periods, which could explain part of the increase in incidence. Information from the hospital records indicate that cirrhosis and alcohol abuse among the male cases in the three largest cities are more common than in the remainder of Sweden. (Author abstract) (15 Refs)

3. CANCER IN INDONESIA.

Sutnick AI, Gunawan S
Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129
JAMA; 247(22):3087-3088 1982

The health care system in Indonesia is outlined and analyzed briefly, and cancer incidence is discussed. Based on 'household survey techniques used from 1972-1980, the rising importance of cancer is suggested. Cancer of the uterine cervix and breast are the two most common types of cancer in Indonesia; cancer of the nasopharynx, liver, skin (especially of the legs and feet) and lung and choriocarcinoma are among the 10 most frequent. Various environmental factors that might influence cancer statistics are mentioned. The government of Indonesia is addressing the growing cancer problem through various programs. (2 Refs)

4. EPIDEMIOLOGY OF HEPATIC, GALL BLADDER, AND PANCREATIC CANCER IN JAPANESE.

Aoki K, Sasaki R
Dept. Preventive Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nippon Rinsho; 40(1):8-14 1982

Factors affecting the occurrence of hepatic, gall bladder, and pancreatic cancer were studied epidemiologically using death statistics. Of the three types of cancer, the age-adjusted death rate for both men and women between 1950-1978 was highest for hepatic cancer. The death rate for hepatic cancer between 1960-1975, was fairly steady for men, and was decreasing for women. There was a slight creeping up of rate between 1975-1978 in both men and women. The rates of death due to pancreatic or choledochal cancer showed an increase in both groups. According to birth cohorts, little change in death rates due to cancer were observed in the men born between 1890-1930. The death rates have decreased for the birth cohorts of women born since 1900. Deaths due to choledochal cancer increased for both men and women between 1969-1978. Higher rates of hepatic cancer were observed in both men and women living in Kyushu and Yamagata Prefecture, in men living in Hiroshima and Osaka, and in women living in Tokushima. Death rates due to pancreatic cancer were high in Hokkaido and Aomori Prefecture. Although none of the three organs has direct contact with the outside environment, there is an increase in environmental carcinogenic factors. It was of interest that latent or complicated infections were observed frequently associated with the cancers. (43 Refs) (In JPN)

5. PRIMARY BILIARY CIRRHOSIS: AN INCREASED INCIDENCE OF EXTRAHEPATIC MALIGNANCIES?

Mills PR, Boyle P, Quigley EM, Birnie GG, Jarrett F, Watkinson G, MacSween RN
Gastroenterology Unit, Royal Infirmary, Glasgow G4 OSF, Scotland
J Clin Pathol; 35(5):541-543 1982

In a retrospective review of 85 patients with primary biliary cirrhosis (PBC), 10(11.8%) were noted to have extrahepatic malignant neoplasm. In seven female patients the tumor developed within a mean of 3.5 yr after the clinical onset of PBC. This observed number of tumors, 3.5x more common than the expected age-adjusted incidence, was statistically significant at the 0.5% level. (Author abstract) (13 Refs)

6. THOROTRAST TUMORS (MEETING ABSTRACT)

Saragoca A, Perpetua M, Oliveira R, Da Silva Horta J
University of Lisbon and Pathological Institut, Lisbon, Portugal
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

The authors studied the frequency of malignant liver tumors in the necropsies held in the Pathological Institute of a Central Hospital in Lisbon, and did a screen of those previously injected with ThO2. Thorotrast is the commercial name of a coloidal suspension of thorium dioxide used as a radiological contrast medium mainly for visualization of blood vessels. Once the drug is injected systemically, it remains in the body, with greatest concentration in the liver, spleen and tributary lymph nodes and to a lesser extent in other RE organs. The AA performed a study in 10.178 necropsies from 1957 to 1980. Among the eighteeen cases of hemangioendothelioma, 17 were injected with thorotrast. Among the twenty cholangiocarcinoma, twelve were previously injected with thorium dioxide. The authors studied the clinical evolution, the liver function tests and alpha fetoprotein determination, in seventeen cases of tumors (2 hepatocellular carcinoma, 9 cholangiocarcinoma and 6 hemangioendothelioma). The AA conclude that the hemangioendothelioma is the malignant liver tumor more frequent among patients injected with thorotrast. On the other side hepatocellular carcinoma is the less frequent. Cholangiocarcinoma, although not as frequent as hemangioendothelial is present in 60% of the patients injected with thorotrast. All these patients have the same clinical evolution: slight dyspeptic complaints for 25 to 40 years, after thorotrast injection. When loss of appetite, weight loss, right upper abdomen pain, jaundice and ascites begun, death occurred in 3 to 9 months from onset of the symptoms. Biochemical data of these patients disclosed high values of alkaline phosphatase, aspartate serum transaminase, gammaglutamyltranspeptidase and alpha 1 and gammaglobulins. (no Refs)

7. A CASE-CONTROL DIETARY STUDY OF PRIMARY LIVER CANCER RISK FROM AFLATOXIN EXPOSURE.

Bulatao-Jayme J, Almero EM, Castro CA, Jardeleza TR, Salamat LA
Food and Nutrition Res. Inst., PO Box EA 467, Ermita, Manila 2801, Philippines
Int J Epidemiol; 11(2):112-119 1982

The dietary intakes of 90 confirmed primary liver cancer cases were compared against 90 age-sex matched controls. Dietary recall, obtained by the same nutritionist, was taken for each change of residence lasting 1 yr or more. The frequency and amounts of food items consumed were calculated into units of aflatoxin load per day using a Philippine table of aflatoxin values of these items. Of the total subjects' aflatoxin load, 51.2% came from cassava, 20.3% from corn, 6.8% from peanuts and 5.8% from sweet potato. The mean aflatoxin load per day of the cases as found to be 440% that of the controls. Upon grouping dietary aflatoxin loads (and alcohol intakes) into Heavy and Light, and upon comparing cases versus controls, the relative risk (RR) of developing primary liver cancer was found to be statistically significant in the following order of rank: cassava, peanuts, sweet potato, corn and alcohol. Boiled rice which had negligence aflatoxin content gave no difference in risk. Combining aflatoxin load and alcohol intake gave a synergistic and a statistically significant effect on RR with Light Aflatoxin, Light Alcohol as RR = 1. Results: Light Aflatoxin, Heavy Alcohol RR = 3.9; Heavy Aflatoxin, Light Alcohol RR = 17.5; Heavy Aflatoxin, Heavy Alcohol RR = 35.0. (Author abstract) (25 Refs)

8. DATA ON THE CARCINOGENICITY OF VINYL CHLORIDE.

Byczkowska Z
Klinika Chorob Zawodowych, Instytut Medycyny Pracy w Przemysle Weglowym i Hutniczym, ul. Bieruta 20, 41-200 Sosnowiec, Poland
Pol Tyg Lek; 37(3):95-97 1982

The case of a patient who developed solid hepatic adenocarcinoma after intermittent exposure to vinyl chloride (VC) for 17 yr is reported, and literature on the carcinogenicity of VC is reviewed. Hepatic angiosarcoma is considered a typical tumor developed from the exposure to VC. Other tumors, such as hepatoma, nephroblastoma, adenosarcoma, adenocarcinoma, epidermoid carcinoma, and fibroangioma were also observed in humans or experimental animals following exposure to VC. (35 Refs) (In POL)

9. A REVERSE RELATIONSHIP BETWEEN EXPOSURE AND LATENCY IN CHEMICALLY INDUCED LIVER CANCER (MEETING ABSTRACT)

Tamburro CH, Greenberg RA
Department of Medicine, University of Louisville, Louisville, KY
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

It is generally believed that the latency period in cancer development is inversely correlated to the duration of exposure, ie, the longer the exposure, the shorter the latency. Vinyl chloride (VC) induced hepatic angiosarcoma (HA) in humans has allowed study of this relationship in 21 North American cases (NA) and 62 worldwide (WW) reported cases. In all HA cases, VC exposure began between 1941 and 1966; 92% of NA and WW cases had long exposures (LE) (10-33 yrs); 7 cases (8%) had short exposures (SE) (3.5 to 7 yrs). The mean duration in both LE and SE groups was 18.5 yrs with two peaks at 15 and 21 yrs. All (100%) HA cases had greater than 9 yrs latency (9 to 39 yrs) with two peaks occurring at 15 and 25 yrs. Deaths from VC related HA began in 1955, increased to more than one/yr after 1967, peaked in 1976 and have rapidly fallen thereafter. Occurrence peaks were first reached in Canada in 1973 and in USA-1974, France-1976, and Germany-1978. Plant operations began in Canada in 1941; USA in 1939-44; France, 1941-57; and Germany, 1952-60. Reported exposure levels were in ranges of 2000 ppm in the 1940's; 200-500 ppm in 1950's; 50-500 ppm in the early 1960's and 50-250 ppm in the late '60's and early '70's; and about 1 ppm after 1974. Individual latencies showed a direct correlation between total exposure and clinical onset of HA, ie, lower total exposure-shorter latency. This held true for SE and LE groups in both the NA and WW cases. (no Refs)

TUMOR INDUCTION IN ANIMALS

10. CHOLANGIOCELLULAR CARCINOMAS INDUCED IN SYRIAN GOLDEN HAMSTERS ADMINISTERED AFLATOXIN B1 IN LARGE DOSES.

Moore MR, Pitot HC, Miller EC, Miller JA
(c/o Miller) McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., 450 North Randall Ave., Madison, WI, 53706
JNCI; 68(2):271-278 1982

The hepatocarcinogenicity of aflatoxin B1 (AFB1) was compared in male Syrian golden hamsters and inbred F344 rats. AFB1 was administered by gavage 5 days/wk for 6 wk at doses of 1 and 2 mg/kg body wt/day to rats and hamsters, respectively; rats did not survive beyond 3 wk with doses of 2 mg/kg/day. After 6 wk the animals either received no further treatment or were given 0.1% phenobarbital sodium in the drinking water. ATPase-deficient foci of hepatic parenchymal cells, neoplastic nodules, and hepatocellular carcinomas were observed in liver sections from AFB1-treated rats killed at 6, 14, or 23 wk; they were not seen in sections from AFB1-treated hamsters killed at 6, 14, or 46 wk. Each of the 50 AFB1-treated rats developed hepatocellular carcinomas by 46 wk; many also had cholangiocarcinomas and mixed hepatocellular-cholangiocellular carcinomas. Hepatocellular carcinomas were found in only 2 of 49 AFB1-treated hamsters by 78 wk. At this time cholangiomas were found in 15 hamsters, and microscopic cholangiomas were seen in all of the livers. Compared to the rat, the hamster was resistant to the hepatotoxic and hepatocellular carcinogenic effects of AFB1. (Author abstract) (32 Refs)

11. COMPARATIVE CARCINOGENICITY OF O-TOLUIDINE HYDROCHLORIDE AND O-NITROSOTOLUENE IN F-344 RATS.

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Lett; 16(1):103-108 1982

The carcinogenicity of o-toluidine hydrochloride (TOL) and o-nitrosotoluene (NTOL) in F-344 rats was evaluated. Mean weights were somewhat lower in the TOL and NTOL groups than in the control group. The mean daily doses of TOL and of NTOL (administered in the diet) were 0.062 g and 0.051 g, respectively. Food consumption was slightly less in the treated animals than in the animals fed the control diet. NTOL was significantly more effective than TOL in inducing hepatomas and bladder papillomas but was less active in the induction of mammary fibroadenomas. Both compounds induced significant numbers of fibromas of the skin and spleen as well as peritoneal tumors. The sc tumors were fibromas or mammary fibroadenomas. The peritoneal tumors were mesotheliomas and low grade spindle cell sarcomas. All invaded deeply into various abdominal organs and the muscular wall of the cavity. Most liver tumors were highly malignant hepatocarcinomas. Two rats displayed enormous multiple metastases of hepatoma tissue to the lungs. Bladder and pelvis-of-kidney tumors were of the usual transitional epithelium type. These results suggest that N-oxidation is important in the induction of bladder and liver tumors, while other metabolic conversions may play a role in the induction of other tumor types observed. (15 Refs)

12. COMPARATIVE TUMOR INITIATING ACTIVITIES OF N-NITROSOMETHYLBENZYLAMINE AND N-NITROSODIMETHYLAMINE IN RAT LIVER.

Labuc GE, Archer MC
(c/o Archer) Dept. Medical Biophysics, Univ. Toronto, Ontario Cancer Inst., 500 Sherbourne St., Toronto M4X 1K9, Canada
Carcinogenesis; 3(5):519-523 1982

The tumor initiating activities of nitrosomethylbenzylamine (NMBzA), an esophageal carcinogen, and nitrosodimethylamine (NDMA), a hepatocarcinogen, were compared in rat liver using modifications of the initiation assays of Tsuda et al and Pitot et al. Equimolar doses of NMBzA or NDMA (33.5 umol/kg) were injected ip into male Sprague-Dawley rats 18 hr after partial hepatectomy. Following selection, foci of preneoplastic hepatocytes were detected by histochemical staining for gamma-glutamyltranspeptidase. Nitrosomethylamylamine (NMAmA, 115 umol/kg), also an esophageal carcinogen, was tested in the assay of Tsuda et al, and nitrosodimethylamine (NDEA, 33.5 umol/kg), a hepatic and esophageal carcinogen, was tested in the assay of Pitot et al. Both NDMA and NDEA induced significant increases in the number of preneoplastic foci above background. In contrast, neither NMBzA nor NMAmA increased the number of foci above background. Microsomes from regenerating liver had a lower capacity to metabolize both NDMA and NMBzA compared to microsomes from intact liver, but the decrease in activity was similar for both compounds. Neither NDMA nor NMBzA significantly inhibited the first wave of DNA synthesis in vivo in the regenerating liver. The results demonstrate that in contrast to NDMA and NDEA, NMBzA and NMAmA lack tumor initiating activity in the liver. (Author abstract) (37 Refs)

13. HISTOGENESIS OF BILE DUCT CARCINOMA ARISING IN OPISTHORCHIS VIVERRINI INFECTED HAMSTERS GIVEN A SINGLE ORAL DOSE OF DIMETHYLNITROSAMINE (MEETING ABSTRACT)

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Department of Medical Helminthology, London School of Hygiene and Tropical Medicine, St. Albans, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Intrahepatic bile duct carcinoma appears to be associated with Opisthorchis viverrini infection in man. Long term superinfections in hamsters of up to 20 months duration do not result in hepatic tumors. Thamavit et al however produced a 100% incidence of cholangiocarcinomas by administering 0.0025% dimethylnitrosamine (DMN) to O viverrini infected hamsters. In this study a dose of DMN expected to induce a low incidence of cholangiocarcinoma in hamsters was chosen. Control hamsters and hamsters receiving 50 O viverrini metacercariae 40 days previously were each given 1.6 mg DMN orally. Mortality was significantly higher in the group receiving both DMN and parasites. Intrahepatic cholangiocarcinomas were found only in animals receiving both parasites and DMN. All tumors were mucin secreting and goblet cell metaplasia was a common feature. Tumors with an acinar type pattern contained an abundant connective tissue stroma and parasite egg granulomas were occasionally found in this stroma. Cholangiofibrosis and cystic cholangiomas were common in both groups, though cholangiofibrosis was more extensive in the group receiving both parasites and DMN. Cholangiocarcinomas appeared to arise either from hyperplastic processes in the bile duct wall or from areas of cholangiofibrosis distinct from major bile ducts. In both cases a range of transitional stages between hyperplasia and carcinoma were seen. Cholangiocarcinoma and cystic cholangioma were frequently seen in close proximity and appeared to have their origin in adjacent areas of cholangiofibrosis. (3 Refs)

14. DINITROTOLUENE PROMOTION OF DIETHYLNITROSAMINE (DEN) INITIATED HEPATOCYTES IN VIVO (MEETING ABSTRACT)

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Toxicologist; 2(1):100 1982

Technical grade DNT (dinitrotoluene) (tDNT) is a potent hepatocarcinogen when fed to F-344 male rats for one year (100% incidence of hepatocellular carcinomas). The present studies were designed to ascertain whether tDNT had promoting activity and to investigate the mechanism of tDNT promotion. Male F-344 rats were treated with a single dose of DEN (150 mg/kg), permitted to recover for 2 wk, and then fed tDNT in the diet for 3 wk. Promotion activity was quantitated by determining the incidence of histochemically identifiable hepatic gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 14 mg/kg/day and 35 mg/kg/day of tDNT caused a dose-dependent increase in GGT+ foci relative to initiation control and promotion control values. To investigate the mechanism of tDNT promotion, the effectiveness of tDNT (35 mg/kg/day) as a replacement for 2-acetyl-aminofluorene (2-AAF) in a hepatic 'growth selection' protocol and its ability to alter DNA synthesis in hepatocytes following partial hepatectomy (PH) were determined. tDNT was active in the growth selection protocol but not as effective as 2-AAF. When tDNT was fed (35 mg/kg/day) for 2 wk prior to PH, it had no effect on the kinetics of DNA synthesis following PH. (no Refs)

15. ASSESSMENT OF THE CAPACITY OF 3,3',4,4',5,5'-HEXABROMOBIPHENYL TO SERVE AS A PROMOTER OF HEPATOCARCINOGENESIS (MEETING ABSTRACT)

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Toxicologist; 2(1):99 1982

The objective of this study was to determine if 3,3',4,4',5,5'-hexabromobiphenyl (HBB) can act as a promoter of hepatocarcinogenesis. This congener and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are similar in that they both cause 3-methylcholanthrene type induction of hepatic microsomal drug-metabolizing enzymes and produce a similar and characteristic pattern of toxic and histologic responses. TCDD has been shown to be a promoter of hepatic cancer in rats. To test the tumor promoting capacity of HBB, female Sprague-Dawley rats weighing 200-250 g were injected ip with diethylnitrosamine (DEN) at a dose of 10 mg/kg 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after PH, groups of 6 rats were fed control diets or diets containing 1 ppm HBB or 500 ppm phenobarbital (Pb). Groups of 3 rats without prior hepatectomy or DEN were fed the same diets. At 6 months, rats were killed and samples were collected for histologic and histochemical evaluation. Gamma glutamyl transpeptidase (GGT) was used to identify enzyme altered foci. The average number of GGT positive foci/cm2 were: control, 0; Pb, 58; HBB, 79. Values for rats not hepatectomized or given DEN were: control, 0; HBB, 11. Rats fed HBB had decreased weight gain and thymic atrophy. Histologically, the liver had severe hepatocellular swelling and vacuolation and focal areas of necrosis. (no Refs)

16. CARCINOGENICITY STUDY OF THE PESTICIDE MALEIC HYDRAZIDE IN MICE (MEETING ABSTRACT)

Cabral JR, Ponomarkov V, Tomatis L
International Agency of Research on Cancer, Lyon, France
Toxicologist; 2(1):62 1982

The carcinogenicity of the pesticide Maleic Hydrazide (MH) was studied in C57BL/B6 mice. The free acid of MH was used (98.5% pure; containing 0.6 ppm of hydrazine impurity). The carcinogenicity experiments with MH included: a) subcutaneous (sc) administration to 163 infant mice (5, 10, 20 and 20 mg MH per mouse on days 1, 7, 14 and 21 after birth, respectively); and b) oral administration (gavage) to 82 male and female mice, from weaning for life, at a weekly dose of 510 mg/kg bw MH. Groups of untreated and solvent controls were also available. The experiments were terminated at 120 weeks. The sc administration to infant mice resulted in high preweaning mortality when compared with the respective controls. Liver-cell tumors were observed in 7 males treated sc with MH. In the solvent-treated (tricaprylin) males, 3 liver-cell tumors were also found. One liver-cell tumor was seen in untreated male controls. No liver-cell tumors were observed in treated or control females. The difference in the incidence of liver tumors among the various groups was not significant. When MH was administered orally (weekly for life), liver-cell tumor were observed in 4 males and in 2 females of the treated group, and in 1 male and in 1 female of the solvent (olive oil) control group. In the respective untreated controls 1 male had a liver-cell tumor. The incidence of tumor at sites other than the liver was similar in all groups. These results partially confirm the negative finding of a recent parallel study in rats. (1 Ref)

17. TRANSPLANTATION STUDIES WITH SPONTANEOUS AND INDUCED MOUSE HEPATIC NODULES (MEETING ABSTRACT)

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Toxicologist; 2(1):97 1982

The present research was designed to assess the potential for progressive growth of hyperplastic, adenomatous and carcinomatous mouse liver lesions grafted into syngeneic hosts and to determine the effect of treatment type, donor age and metastatic potential on this parameter. Lesions were obtained from male B6/C3F1 mice fed chow or chow mixed with a chlorinated hydrocarbon pesticide (DCB). Animals were sacrificed at 18 or 24 months of age. Hosts were sacrificed at 8 months, or when grafts reached 2cm in diameter. Lesions diagnosed as non-malignant (hyperplastic or benign) were more likely to grow after transplantation if obtained after 24 months, rather than after 18 months. There was a close correlation between donor lesion morphology and ability to grow in a recipient mouse. The majority of lesions retained the morphological appearance of the donor lesions. Transplanted lesions from control mice were more likely to grow than were those from DCB treated mice. This correlation was particularly strong for hyperplastic nodules. Metastatic capability in the donor animals correlated positively with both growth potential and growth rate in recipient mice. These findings suggest that progression toward autonomous growth may occur both within the original host and during a prolonged transplantation period, making data interpretation difficult. Lesion morphology alone may not be adequate for assessing capacity for autonomous growth. (no Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

18. INHIBITION OF THE HEPATOCARCINOGENIC ACTIVITY OF DIETHYLNITROSAMINE (DENA) BY ETHANOL IN RATS.

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Hepatogastroenterology; 28(5):242-244 1981

Male Sprague-Dawley rats received 0.1 mg/kg of diethylnitrosamine orally 5 times a wk for life with or without additional subsequent administration of 5 ml/rat/day of a 25% aqueous solution of ethanol. The additional treatment with ethanol significantly reduced the induction of liver cancer, but not of esophageal tumors. These findings do not support speculations based on epidemiologic studies as to a cancer-causing effect of alcohol. (Author abstract) (11 Refs)

19. CHOLECYSTOKININ INHIBITS NITROSAMINE-INDUCED CARCINOGENESIS (MEETING ABSTRACT)

Johnson FE, LaRegina MC, Martin SA, Bashiti HM
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Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Acute administration of cholecystokinin (CCK) has well-known effects on gall bladder contractions and pancreatic-biliary secretion. Recent data indicates that chronic administration of CCK has trophic effects on abdominal viscera, particularly pancreas. In order to determine whether CCK enhances malignant growth as well as growth of normal organs, we administered CCK together with di-isopropanol nitrosamine (DIPN), a carcinogen known to induce pancreatic, hepatic (and other) carcinomas. Two hundred young male Syrian golden hamsters (approx 60 gm) were divided into four groups. Group A (80 animals received DIPN (250 mg/kg) plus CCK (20 U/kg) by weekly subcutaneous injections; Group B (80 animals), DIPN alone; Group C (20 animals), CCK alone; Group D (20 animals), saline. Injections were done for 40 weeks, with animal sacrifice and autopsy at 10, 14, 18, 27, and 40 weeks. Microscopic study of pancreas, liver, heart, lung, brain, spleen small intestine, large intestine, testis, kidney, and stomach was carried out in each animal. Animal weights and visceral weights showed no striking differences between groups. Microscopic examination of the pancreas showed: DIPN induced pancreatic and hepatic carcinomas; CCK administration appeared to prevent their development. The mechanism of this effect is unknown. These results have implications for human carcinogenesis, and some of the implications are testable by currently available methods. (no Refs)

20. EFFECT OF IMMUNIZATION OF RATS WITH HUMAN ALPHA-FETOPROTEIN (AFP) UPON THE DEVELOPMENT OF HEPATOMA BY 3'-METHYL-4-DIAMINOAZOBENZENE (MEETING ABSTRACT)

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Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

It has been demonstrated that the administration of anti-rat AFP horse serum inhibited the elevation of serum AFP and the development of hepatoma by 3'-Me-DAB (3'-methyl-4-diaminoazobenzene) (passive immunization). It has also been known that when animals are immunized with AFP which is heterologous to that animal, they produce antibodies both to the heterologous AFP and to their own AFP (active immunization). In this study rats were immunized with human AFP and its effect upon serum AFP levels and development of hepatoma by 3'-Me-DAB was investigated. Rats immunized with 0.5 mg human AFP with Freund's complete adjuvant produced the antibody both to human and rat AFPs, the titers of which were 8-64 times and 2 times respectively. These rats were fed 3'-Me-DAB containing diet. At the time of hepatoma development 8 out of 10 control rats showed elevated serum AFP levels, and died of tumor in 21 weeks. On the other hand, in the immunized rats only 2 out of 6 showed elevated AFP and died of tumor. But 4 rats maintained low AFP levels and survived. No tumor was detected in survived rats which were sacrificed in the 30th week. (no Refs)

21. COCARCINOGENICITY OF SACCHARIN TOWARD N-DIBUTYL-NITROSAMINE CARCINOGENICITY IN RAT LIVER AND URINARY BLADDER (MEETING ABSTRACT)

Pereira MA, Britt AL
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Toxicologist; 2(1):64 1982

Saccharin has been demonstrated to be a promoter of chemical carcinogenesis in the rat urinary bladder. Since other tumor promoters are also cocarcinogens, we evaluated the possibility that saccharin is also a cocarcinogen. Male Fisher 344 rats simultaneously received 0.02% dibutylnitrosamine (DBN) in their drinking water and 5% sodium saccharin in their diet for a total of 26 weeks. The liver of rats that received only DBN contained 16 hyperplastic nodules among 5 of 29 (17%) animals and 2 hepatocellular carcinomas in 1 of 29 (3%) of the animals. The simultaneous administration of sodium saccharin to the animals that received DBN, produced an enhanced hepatocarcinogenic response of 106 hyperplastic nodules in 17 of 21 (81%) animals and 81 hepatocellular carcinomas in 17 of 21 (81%) animals. The number of preneoplastic focal alterations in the liver that were induced by DBN, was also enhanced by sodium saccharin. The livers of untreated control rats and rats that received only sodium saccharin were free of preneoplastic foci, hyperplastic nodules and hepatocellular carcinomas. In the urinary bladder, treatment with DBN produced simple and nodule hyperplasia that was enhanced by simultaneous treatment with saccharin. Sodium saccharin did not result in either a preneoplastic hyperplasia or a neoplastic response in the urinary bladder of the rats. (no Refs)

22. PROMOTION OF LIVER TUMORS IN B6C3F1 MALE MICE BY PARTIAL HEPATECTOMY OR DIETARY CHOLINE DEFICIENCY (MEETING ABSTRACT)

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Toxicologist; 2(1):63 1982

Groups of male weanling B6C3F1 strain of mice were fed a control semisynthetic diet (C) or the same diet devoid of choline (CD). Some mice from each group were subjected to partial hepatectomy (HepX) after two weeks on diet. Sequential sacrifices of mice from each group revealed the following: after three months, no tumors in any mice although the CD mice had enzyme deficient and fat-free islands of proliferating hepatocytes; after six months choline deficient mice only had liver tumors; after nine months control mice, 0% tumors, C+HepX mice 20% tumors, CD mice 100% tumors and CD+HepX mice 40% tumors. Autoradiographic studies indicated that both HepX and CD increased DNA synthesis and liver cell proliferation at all periods examined. These data suggest that the liver of B6C3F1 mice is sensitive to agents or conditions which are not tumorigens themselves but which may promote tumors. (no Refs)

23. THE EFFECT OF DEPRIVATION OF HEPATIC BLOOD SUPPLY ON THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RAT (MEETING ABSTRACT)

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Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

The aim of the experiment is to study the role of portal venous blood and hepatic arterial blood on the growth of hepatocellular carcinoma in rats exposed to carcinogens prior to deprivation of hepatic blood supply. Clinical evidence indicates that shrinkage of tumor may occur after protocaval shunt and hepatic artery ligation. Male Sprague Dawley rats weighing between 250 grams to 300 grams were used. They were given diethylnitrosamine in their drinking water at a dosage of 10 mg/kg/day for 10-16 weeks. Randomly the rats were then assigned to one of the 3 groups for operation under ether anesthesia. Fifty-six rats had end-to-side portocaval shunt, 25 rats had ligation and division of the hepatic artery, 20 rats had a sham operation. At the time of the operation, no tumor was found in the liver. After the operation, carcinogen were stopped and the rats were killed 10-12 weeks later. Fifty per cent of the operated rats survived for a period of 10-12 weeks and were suitable for morphometric assessment; 22 rats in the portocaval shunt group, 15 rats in the hepatic artery ligation group, and 11 rats in the sham operation group. The size of the hepatocellular carcinoma in the shunt group was significantly greater than the tumor in either the hepatic artery ligation group or the sham operation group. There was no difference between the last groups. End-to-side portocaval shunt in rats previously exposed to carcinogen enhances the growth of hepatocellular carcinoma. This may be due to either the diversion of factors in the portal blood which suppress tumor growth, or the atrophy of liver cords after shunting or increased hepatic arterial flow enhances tumor proliferation. (no Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

24. COVALENT BINDING OF BENZIDINE AND N-ACETYLBENZIDINE TO DNA AT THE C-8 ATOM OF DEOXYGUANOSINE IN VIVO AND IN VITRO.

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Cancer Res; 42(7):2678-2686 1982

Benzidine, a human urinary bladder carcinogen, induces hepatic tumors in mice and rats. In this study [3H]benzidine was administered in drinking water to mice for 1 wk, and the covalent binding of the carcinogen to hepatic DNA was then determined. A single carcinogen: DNA adduct was detected which decreased in concentration by approx 50% at 1 day after treatment and then remained at a nearly constant level for at least 7 days. Injection of radiolabeled benzidine or N-acetylbenzidine into rats also resulted in a single carcinogen:DNA adduct that was chromatographically identical to that obtained in mouse liver. While administration of benzidine and N-acetylbenzidine resulted in high levels of the adduct in rat hepatic DNA, injection of N,N'-[ring-14C]diacetylbenzidine did not give detectable binding. The same carcinogen:DNA adduct found in rat and mouse liver was prepared synthetically by: (a) hydrolysis of calf thymus DNA reacted with N-hydroxy-N'-acetylbenzidine at pH 5; and (b) reaction of N-acetoxy-N,N'-diacetylbenzidine with deoxyguanosine and subsequent selective deacetylation of the product with methanolic ammonia. Mass and nuclear magnetic resonance spectral data of the synthetic products established the structure of the hepatic adduct as N-(deoxyguanosin-8-yl)-N'-acetylbenzidine. The nonacetylated derivative, N-(deoxyguanosin-8-yl)benzidine, was synthesized by carboxylesterase treatment of N-(deoxyguanosin-8-yl)-N'-acetylbenzidine and was shown not to occur in rat and mouse liver DNA. These data indicate that the metabolic activation of benzidine to an ultimate carcinogen in rats and mice does not involve N-hydroxybenzidine or sulfotransferase-catalyzed activation of N-hydroxy-N,N'-diacetylbenzidine. The remaining pathways for metabolic conversion of benzidine to an ultimate carcinogenic species are discussed in relation to liver and urinary bladder carcinogenesis. (46 Refs)

25. METABOLISM AND NUCLEIC ACID BINDING OF 7-FLUORO-2-ACETAMIDOFLUORENE IN RATS: OXIDATIVE DEFLUORINATION AND APPARENT DISSOCIATION FROM HEPATOCARCINOGENESIS OF 8-(N-ARYLAMIDE)GUANINE ADDUCTS ON DNA.

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Chem Biol Interact; 40(1):27-43 1982

The significance in hepatocarcinogenesis of various arylamine/amide adducts with nucleic acid was investigated. Female Fischer and Sprague-Dawley rats are comparably sensitive to hepatocarcinogenesis by 2-acetamidofluorene (AAF), while male rats are more sensitive. 7-Fluoro-2-acetamidofluorene is more carcinogenic in Sprague-Dawley rats than is AAF, and strikingly so toward the liver of female rats. Binding of both compounds to liver nucleic acids was determined for Fischer rats at 1 and 3 days after a single injection of carcinogen, and in female Sprague-Dawley rats from 1 to 28 days after a single injection. No 8-(N-2-fluorenylacetamido)guanine adduct or the 7-fluoro derivative could be found in RNA or DNA of female Sprague-Dawley rats treated with AAF These adducts were present in comparable amounts in both male and female Fischer rats. The binding of 7-fluoro-AAF derivatives was higher than that of AAF derivatives in female Sprague-Dawley rats. Feeding of either AAF or 7-fluoro-AAF to Sprague-Dawley rats for 4 wk before a single injection of [3H]7-fluoro-AAF resulted in reduction of the 8-(N-2-(7-fluoro)fluorenyl-acetamido)guanine adduct in males to undetectable levels in DNA and to 10% of control level in RNA. Non-acetylated adducts were increased in males, but decreased in females by AAF prefeeding; 7-fluoro-AAF prefeeding resulted in little change in adduct formation in females and in a major increase in non-acetylated adducts in males. AAF adducts disappeared from DNA more rapidly than did 7-fluoro-AAF adducts. Assay of the urinary metabolites from the animals in the prefeeding experiment showed that all compounds fed increased the proportion of N-hydroxy-7-fluoro-AAF among the metabolites. Defluorination of 7-fluoro-AAF to 7-hydroxy-AAF was also demonstrated and the ratio of 7-hydroxy-AAF to 5-hydroxy-7-fluoro-AAF was comparable to that observed for 7-hydroxy-AAF/5-hydroxy-AAF and AAF itself, suggesting that fluoro substitution does not increase activity by preventing detoxication. (28 Refs)

36. METABOLISM AND MUTAGENIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY HUMAN LIVER AND LUNG.

Boobis AR, Brodie MJ, McManus ME, Staiano N, Thorgeirsson SS, Davies DS
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Adv Exp Med Biol; 136(partB):1193-1201 1982

Ability of microsomal fractions of human liver to metabolize 2-acetylaminofluorene (2-AAF) and the capacity of subcellular fractions of human liver and lung to convert 2-AAF and N-hydroxy-2-acetylaminofluorene (N-OHAAF) to mutagens were investigated. Microsomal fractions of human liver were relatively active in metabolizing 2-AAF, total oxidative metabolism being greater than that of male Sprague-Dawley rats. Rank order of activities with human liver was 7-hydroxylation greater than 3-hydroxylation greater than 9-hydroxylation greater than 5-hydroxylation. Thus, man is much more active at N- and 3-hydroxylation of 2-AAF than either rat or Rhesus monkey. In biopsies with preserved hepatic architecture, cigarette smoking was associated with significant increases in arylhydrocarbon hydroxylase (AHH) and 1-acetylaminofluorene 3-hydroxylase (2-AAF-3H) activities but not with any significant change in the other 2-AAF hydroxylases or in total cytochrome P-450 content. The correlation between 2-AAF-3H and AHH was significant (0.778) but both enzyme activities were increased in cigarette smokers. When the correlation coefficient was calculated for the non-smokers it was 0.532. The correlation between 2-acetylaminofluorene 7-hydroxylase and AHH was relatively poor (0.668) but only AHH activity was increased in cigarette smokers. No significant correlation between 2-acetylaminofluorene N-hydroxylase and AHH activities (0.554) could be seen. In non-smokers the correlation coefficient was only 0.452. Human liver microsomal fraction activated both 2-AAF and N-OHAAF into a mutagen, whereas human lung post-mitochondrial fraction activated only N-OHAAF into a mutagen. Considerable inter-individual variation in the ability of human tissue samples to activate 2-AAF into a mutagen was observed. The ability of microsomal fractions of human liver to activate 2-AAF to a mutagen did not correlate with N-hydroxylase activity nor with any other enzyme activity measured. Mutagenic activation of 2-AAF and N-OHAAF was unaffected by cigarette smoking. (16 Refs)

27. MICROSOMAL METABOLISM OF 2-ACETYLAMINOFLUORENE, ROLE IN MUTAGENICITY AND CARCINOGENICITY.

Roberfroid M, Razzouk C, Agazzi-Leonard E, Batardy-Gregoire M, Poncelet F, Mercier M
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Adv Exp Med Biol; 136(partB):921-929 1982

Biochemical properties of microsomal enzymes catalyzing endoplasmic reticulum-mediated metabolism of 2-acetylaminofluorene (2AAF), including reactions of primary activation and detoxification, were studied as means of elucidating the mechanism of biological effects of 2AAF. Correlation of kinetic parameters of liver microsomal N-hydroxylase with carcinogenic effects showed that the rat is the most susceptible species, but exhibited the lowest activity, whereas the mouse is the least susceptible species, but it has the highest enzyme activity. The rat liver microsomal N-hydroxylase showed the highest affinity for 2AAF, whereas the mouse liver enzyme had the lowest affinity. Mutagenicity of the animal microsomal preparations correlated well with their enzyme activities ranking in the order hamster = mouse much greater than rat in terms of the Ames test with 2AAF as a promutagen. Kinetic parameter studies with rat liver microsomal N-hydroxylase showed that 2AAF and 2-aminofluorene modified the enzyme, but other aminofluorene isomers did not. Feeding the rat with 2AAF and 3-methylcholanthrene (3MC) resulted in a competitive inhibition in the endoplasmic reticulum that reduced N-hydroxylating capacity. Similar behavior of 3MC in the hamster results in the initiation of cancer because the hamster liver N-hydroxylase activity is far higher than that of the rat liver enzyme so that there is production of sufficient N-hydroxy-metabolite to initiate cancer. (18 Refs)

28. FORCE FIELD CONFORMATIONAL ANALYSIS OF AMINOFLUORENE AND ACETYLAMINOFLUORENE SUBSTITUTED DEOXYGUANOSINE.

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Chem Biol Interact; 40(1):57-76 1982

The hepatocarcinogen N-hydroxy-2-acetylaminofluorene forms two C8-substituted deoxyguanosine adducts in vivo. The conformation of these adducts, as well as 2'-deoxyguanosine and 8-amino-2'-deoxyguanosine has been studied with Allinger's force field. Using the glycoside rotation as a reaction coordinate, multidimensional potential energy surfaces were determined by relaxing all internal degrees of freedom. The calculations indicate the 2'-deoxyguanosine should exist as a mixture of syn and anti forms, that the syn form is slightly favored for 8-amino-2'-deoxyguanosine, that N-(deoxyguanosin-8-yl)-2-acetylaminofluorene (dG-C8-AAF) will only be found in the syn conformation and that, although the syn form is also more stable for N-(deoxyguanosin-8-yl)-2-aminofluorene (dG-C8-AF), it will have a substantially greater proportion of the anti-conformer than is found with dG-C8-AAF. The results of the force field calculations are discussed in relation to the effects these adducts may have on DNA structure. (Author abstract) (55 Refs)

29. METABOLISM AND TOXICITY OF AFLATOXINS.

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Adv Exp Med Biol; 136(partB):847-863 1982

Recent results and experiments on the toxicity and metabolism of aflatoxins are reviewed. In vitro metabolism of aflatoxin B1 (AFB1), characteristics of the AFB1-2,3-oxide and the dihydrol and hemiacetal of AFB1, AFB1-2,3-oxide formation and animal susceptibility, migration of AFB1-2,3-oxide to target sites, questions concerning the effects of phenobarbital pretreatment in in vivo and in vitro studies, and metabolism and toxicity in primary hepatocyte cultures are discussed. The carcinogenic potency of AFB1 in an animal appears to be due to competing pathways of activation and detoxification in the cells, involving the mixed function oxygenases in the endoplasmic reticulum and nuclear membrane and the reductase, epoxide hydrolase, glutathione transferase, and other enzymes in the cytoplasm. These enzymes appear to be localized intracellularly so that no single in vitro metabolism system is able to simulate the in vivo condition to produce a simple set of metabolic parameters for the prediction of AFB1 toxicity. A battery of in vitro assays may represent a successful approach. (54 Refs)

30. BENZO(A)PYRENE METABOLISM AND ENTEROHEPATIC CIRCULATION IN THE RAT.

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Adv Exp Med Biol; 136(partA):761-768 1982

Enterohepatic circulation of benzo(a)pyrene (BP) metabolites were investigated in rats to determine the availability of potentially toxic metabolites to tissues within this cycle. [14C]-BP (3 uM/kg; 25 uCi/kg or 65 uCi/kg) was administered by iv injection to rats with bile duct cannulae. For enterohepatic recirculation experiments, 2-hr bile samples were collected from anesthetized rats receiving the [14C]-BP. The bile samples containing the [14C]-BP metabolites were cross-transfused into the duodena of bile fistulated rats, and the bile was collected from the recipients. Metabolites from the the bile samples were separated by high pressure liquid chromatography. The major identified metabolites in the bile extract were conjugates and/or polyhydroxylated metabolites, BP 4,5-diol, 9-OH BP, and 3-OH BP/BP 3,6-quinone; the proximate carcinogen benzo(a)pyrene 7,8-diol was not detected in these experiments. When biliary metabolites were cross-transfused to the duodena of bile duct cannulated rats, 18.7 +-6.5% of the dose was re-excreted in the bile within 30 hr. The pattern of metabolites which had been recycled from duodenum to bile was very similar to that in the bile which had been infused. Metabolite A1 (unknown) was, however, only detected after recirculation of metabolites; this metabolite was found to increase in relative amount in the bile of rats where there was minimal interference to the enterohepatic circulation. As the process of enterohepatic circulation necessitates the transfer of biliary metabolites, which are mutagenic, though the intestinal wall, it is possible that the metabolites or their secondary products could react with nucleophilic sites in the intestinal wall. (13 Refs)

31. THE RELATIONSHIP BETWEEN THE METABOLISM AND TOXICITY OF BENZODIOXOLE.

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Adv Exp Med Biol; 136(partB):881-893 1982

Safrole metabolites are discussed in terms of their effects on cytochrome P-450 dependent enzyme activities, effects on the endoplasmic reticulum, development of preneoplastic nodules, and appearance of well-differentiated hepatic tumors. The heme of cytochrome P-450 apparently forms a metabolite complex with the benzodioxole compound, probably through an intermediate oxidized carbene metabolite. Benzodioxole compounds also induce a novel form of cytochrome P-450, which along with other species of the enzyme bind to the benzodioxole compounds in the normal liver. The benzodioxole is then metabolized to a ligand complex, leading to inhibition of the cytochrome P-450 mediated metabolism of endogenous lipids. When added to isolated hepatocytes safrole effectively inhibits protein synthesis and causes depletion of glutathione. Safrole can also degranulate rough endoplasmic reticulum when in the presence of NADPH; safrole and isosafrole are known to form metabolites which are found in all major organelles of the rat liver. (44 Refs)

32. EFFECTS OF LINDANE TREATMENT ON DRUG METABOLIZING ENZYMES AND LIVER WEIGHT OF CF1 MICE IN WHICH IT EVOKED HEPATOMAS AND IN NON-SUSCEPTIBLE RODENTS.

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Chem Biol Interact; 40(1):1-14 1982

The specific activities of some enzymes which are thought to be involved in the metabolism of lindane were studied in three different mouse strains in order to investigate whether differences exist in the activities of these enzymes. Because the enzyme pattern may change after lindane treatment during the carcinogenicity studies, we also investigated the enzyme activities in animals treated for 3 days or 3 mo with various doses of lindane. The influence of lindane treatment on the relative liver wt was also determined. Basal glutathione-S-transferase activity was higher in males than in females in all three strains, bearing no apparent relationship to susceptibility for tumor formation. However, after treatment with the highest dose of lindane a five- to six-fold induction of this enzyme activity was observed in female CF1 mice, which then together with the male CF1 mice had a higher glutathione-S-transferase activity than untreated and treated B6C3F1 mice and Osborne-Mendel rats. Whether lindane or one of its metabolites is activated by conjugation with glutathione remains to be established. After treatment of the animals with high doses of lindane detergent-treated rat liver microsomes showed a higher UDP-glucuronosyltransferase activity than mouse liver microsomes. This high activity could lead to a rapid conjugation of phenols derived from lindane. The most striking difference observed in this study was the fact that together with the larger increase in absolute and relative liver wt, untreated and treated CF1 mice showed higher monooxygenase activity and, after treatment with lindane, lower expoxide hydrolase activity than rats. Whether the monooxygenase and epoxide hydrolase activities will lead to an accumulation of reactive epoxides derived from lindane remains to be clarified. (18 Refs)

33. COMPARISON OF MICROSOMAL INDUCER PRETREATMENT ON THE IN VITRO ALPHAHYDROXYLATION AND MUTAGENICITY OF N-NITROSOPYRROLIDINE IN RAT AND HAMSTER LIVER.

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Environ Mutagen; 4(3):221-230 1982

Reasonable agreement is demonstrated between rates of microsomal alpha-hydroxylation of N-nitrosopyrrolidine (NPYR) and the metabolic activation of NPYR to a mutagen by post-mitochondrial supernatants when changes in microsomal protein are taken into account. The Ames assay for mutagenicity was employed with use of Salmonella typhimurium strain TA 1535. Rats and hamsters were pretreated with 3-methylcholanthrene (MC), phenobarbital (PB) or Aroclor 1254 (AR). In the rat, most active post-mitochondrial supernatant preparations were obtained with PB and AR while in hamsters AR was most effective in increasing mutagenicity of NPYR. The influence of the various modifiers of mixed function oxidase activity on protein content was determined on liver subfractions. In the rat, no difference was observed in the protein content of post-mitochondrial or post-microsomal supernatant while all the inducers increased these parameters in the hamster. The same pretreatments were tested on the rate of microsomal alpha-hydroxylation of NPYR. In the rat, only AR pretreatment resulted in significant enhancement, while MC slightly decreased the rate. In the hamster, both MC and AR pretreatment markedly increased the rate. When NPYR alpha-hydroxylase is expressed per g of wet wt of liver, differences in the amount of microsomal protein are included and better agreement between metabolism and mutagenicity in PB pretreated animals is obtained. MC and AR pretreatment increased aldehyde dehydrogenase activity in post microsomal supernatants in both rats and hamsters, while PB only increased the activity in hamster preparations. (26 Refs)

34. THE EFFECT OF SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE (MAO) ON HEPATIC DIMETHYLNITROSAMINE (DMN) METABOLISM AND MUTAGENICITY IN THE AMES TEST (MEETING ABSTRACT)

Lake BG, Rowland IR, Collins MA, Phillips JC, Cottrell RC, Gangolli SD

The British Industrial Biological Research Association, Carshalton, Surrey, SM5 4DS, England

Toxicologist; 2(1):172 1982

Dimethylnitrosamine (DMN), a potent hepatocarcinogen and mutagen, requires metabolic activation to exert its biological effects. Although it has been suggested that hepatic DMN metabolism is catalyzed by cytochrome P-450 dependent mixed function oxidase (MFO) enzymes, recent studies have provided evidence for several pathways of DMN metabolism. We have investigated the effect of a number of substrates and inhibitors of monoamine oxidase (MAO, EC 1.4.3.4) on DMN metabolism and DMN-induced mutagenicity. The metabolism of DMN for formaldehyde by rat hepatic postmitochondrial supernatant fractions was markedly inhibited by a number of MAO inhibitors (eg aminoacetonitrile, benzyl cyanide, indazole and pargyline) and by MAO substrates (eg benzylamine, 2-phenylethylamine, tryptamine and tyramine), but not by the deaminated aldehyde, acid and alcohol products of the latter class of compounds. At the concentrations which inhibited DMN metabolism the MAO substrates and inhibitors had little effect on a range of MFO enzyme activities. While the mutagenicity of DMN in the Ames test was markedly inhibited by MAO substrates and inhibitors, these compounds had little effect on the mutagenicity of either aflatoxin B1 or benzo(a)pyrene. (no Refs)

35. COMPARATIVE BIOCHEMISTRY AND METABOLISM. PART 1. CARCINOGENESIS. ANNUAL REPORT, JUN. 1980-MAY 1981.

Shank RC
Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, Ohio
Sci Tech Aerosp Rep; 20(8):1128-1129 1982

Oral administration of the inorganic hepatotoxin, hydrazine, to male Fischer 344 or Sprague Dawley rats results in the endogenous methylation of liver DNA at the 7-and O6-positions of guanine. At doses below the LD50 (45, 60 or 75 mg hydrazine/kg body wt), methylation levels varied little and averaged about 500 micromol 7-methylguanine/mol guanine and 20 micromol O6-methylguanine/mol guanine. At 90 mg hydrazine/kg body wt (approx the 7-day LD50) the methylation levels were 869 micromol 7-methylguanine and 58 micromol O6-methylguanine/mol guanine 24 hr after toxicant administration. A single dose of 3 mg hydrazine/kg body wt did not result in detectable levels of methylguanines in liver DNA; however, after three or four daily administrations of hydrazine at this dose, liver damage was evident, and liver DNA contained 50-100 micromol 7-methylguanine/mol guanine, about the limit of analytical detection. Following a single oral administration of 90 mg hydrazine/kg body wt, liver DNA guanine rapidly became methylated. The time for half-maximum alkylation of 7-guanine was 30 minutes and at O6-guanine, 45 minutes. The rates of removal of these methylated bases were consistent with published values from experiments using methylating carcinogens and with values obtained in this laboratory with the model compound, 1,2-dimethylhydrazine. (Author abstract)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

36. EVIDENCE THAT HEPATITIS B VIRUS HAS A ROLE IN LIVER-CELL CARCINOMA IN ALCOHOLIC LIVER DISEASE.

Brechot C, Nalpas B, Courouce AM, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P
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N Engl J Med; 306(23):1384-1387 1982

Determinations of hepatitis B virus (HBV) DNA were made in a prospective study of 51 alcoholics without hepatocellular carcinoma (HCC) and in a retrospective study of 20 alcoholics with both alcoholic cirrhosis and HCC. The overall prevalence of HBV serologic markers was 37% in the first group, compared with 10% in a nonselected blood-donor population. HBV DNA was detected in liver samples from three hepatitis B surface antigen (HBsAg)-positive patients from the first group and in liver samples of five other patients from this group in whom serum HBsAg was not detectable. In the second group, HBV DNA was detected in the neoplastic portion of the autopsied liver in all patients. Integration of viral DNA into the hepatocellular DNA was demonstrated in the samples from the second group, but conclusively in only two samples from the first group. HBV DNA was not detected in the livers of 14/16 patients with alcoholic liver disease (from the first group) who were negative for HBsAg but positive for anti-hepatitis B core antigen or anti-HBsAG, suggesting that HBV is probably not involved in progression of the liver disease. The presence of HBV DNA in livers of alcoholic patients without HCC may delineate the population at high risk for development of this disease. (25 Refs)

37. HEPATITIS B AND PREVENTION OF HEPATOCELLULAR CARCINOMA.

Blumberg BS
Inst. for Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Nouv Presse Med; 11(12):903-905 1982

The role of a hepatitis B virus (HBV) vaccine in the prevention of hepatocellular carcinoma (HCC) is discussed. Production of the HBV vaccine, the relationship between HBV and HCC, and viruses similar to HBV are considered. Geographic regions with a high incidence of HBV surface antigen coincide with areas of high HCC incidence. Infection with HBV is most common among patients presenting with HCC compared to appropriate controls. (no Refs) (In FRE)

38. HEPATITIS-B VIRUS INFECTION IN BLACK CHILDREN WITH HEPATOCELLULAR CARCINOMA.

Kew MC, Hodkinson J, Paterson AC, Song E
Dept. Medicine, Witwatersrand Univ. Medical Sch., Hospital Hill, Johannesburg 2001, South Africa
J Med Virol; 9(3):201-207 1982

Six unselected South African black children (2 female, 15 and 16 yr old; 4 male, 10-13 yr old) with hepatocellular carcinoma (HCC) were examined for hepatitis-B virus (HBV) infection. Characteristics of the tumors were similar to those in black adults. All of the patients were positive for hepatitis B surface (HBs) antigen and hepatitis B core antigen in the serum. Hepatitis Be antigen was present in four patients; sera from the two patients without e antigen (1 male, 1 female) were positive for e antibody. All of the sera were negative for HBs antigen. Taken in conjunction with the HBV status of black adults in South Africa, the findings suggest the possibility that nearly all black patients with HCC are or have been infected with HBV. If HBV is oncogenic, tumor formation may occur within 10 yr of the initial infection. (14 Refs)

39. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K
Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan
Nippon Rinsho; 40(2):468-477 1982

World epidemiological surveys and molecular biology research on the relationship between hepatitis B virus (HBV) and liver cancer are discussed, and cases of hepatitis and hepatic cirrhosis which transformed into hepatic cancer in Japanese patients are analyzed. Various epidemiological and molecular biology studies show a clear correlation between HBV and hepatic cell carcinoma. Patients with B-type hepatitis, cirrhosis, or hepatic cancer were significantly younger than those with non-B type hepatitis, cirrhosis, or hepatic cancer, respectively. Approx 70% of 110 cases of hepatic cancer were found to have positive laboratory findings related to HBV. The patients who had chronic liver disease and who were positive for hepatitis Bs (HBs) antigen were thought to be at high risk for developing hepatic cancer. No direct relationship was observed between alpha-fetoprotein (AFP) levels and serum HBs antigens, however, monitoring levels of AFP was thought to be an important method to help detect early stage liver cancer. (33 Refs) (In JPN)

40. OF WOODCHUCKS AND MEN: THE CONTINUING STORY OF HEPATITIS B AND HEPATOCELLULAR CARCINOMA.

Johnson PJ, Williams R
Liver Unit, King's Coll. Hosp. Medical Sch., London SE5 8RX, England
Br Med J; 284(6329):1586-1588 1982

Statistical evidence that presence of hepatitis B surface antigen (HBsAg) is associated with high rates of hepatocellular carcinoma is presented. Studies on the relationship between HBsAg and cirrhosis lead to the hypothesis that in susceptible people the hepatitis B virus causes either a healthy carrier state or chronic liver disease depending on the host's immunological reaction to the virus. After many years the virus becomes part of the host genetic material, and in some cases this may lead to malignant change. Potential uses of vaccines against hepatitis B virus or antiviral chemotherapy in carriers are discussed. (22 Refs)

41. CHRONIC HEPATITIS AND HEPATOCELLULAR CARCINOMA ASSOCIATED WITH WOODCHUCK HEPATITIS VIRUS.

Snyder RL, Tyler G, Summers J
Penrose Res. Lab., Zoological Society of Philadelphia, Philadelphia, PA
Am J Pathol; 107(3):422-425 1982

The relationship between chronic hepatitis (CH), woodchuck hepatitis virus (WHV), and hepatocellular carcinoma (HCC) was examined. Postmortem study of 1,007 woodchucks killed by hunters revealed 4 animals with HCC and 336 with mild to severe hepatitis. Experimental infections were produced in five animals. The histopathology of woodchuck hepatitis is described and compared with that of human hepatitis B infection. Incidence of HCC in woodchucks with CH and WHV is discussed. (14 Refs)

42. HEPATITIS B VIRUS INFECTION IN HEPATOCELLULR CARCINOMA AND OTHER MALIGNANCIES (MEETING ABSTRACT)

Lim KP, Singh R, Oon CJ
University Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316, Singapore
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Patients with advanced malignant diseases have depressed cell mediated immunity and are vulnerable to various viral and opportunistic infections. Similarly patients with primary hepatocellular carcinoma (PHC) are also known to have a depressed immunity. Seropositive Hepatitis B virus (HBV) infections are common (70-90%) in PHC patients in the Asian Pacific Region and this country. Could this presence of the HBV in such PHC patients be due to a newly acquired HBV infection from a depressed immunity of malignancy or to a pre-existing infection by the HBV virus? We investigated this question in a pilot study on 56 PHC patients and 47 patients with other malignancies. During the period between January to July 1980 the sera of these patients and a random normal control group matched for age and sex were examined. Hepatitis B surface antigen (HBsAg) and antibody to Hepatitis B core antigen (HBcAb) were determined using commercial radioimmunoassay kits. In this study the incidence of HBs antigenemia in PHC patients was found to be higher than in normal individuals or in the tumor control group. In the latter two groups, the incidence of antigenemia was similar. The incidence of HB core antibody was also higher in PHC patients than in normal controls but not significantly different from the other tumor controls. (no Refs)

43. HEPATITIS B E ANTIGEN AND ANTIBODY TO HEPATITIS B E ANTIGEN IN THE PATIENTS WITH PRIMARY HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT)

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2nd Department of Internal Medicine, Kyoto University School of Medicine, Kyoto, Japan
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

A close association between heptitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC) has been noted. Therefore, to gain further insight into this relationship, we undertook the present study. First, we looked for the prevalence of HBeAg and antibody to HBeAg (HBeAb) in the patients with HCC and compared the results in asymptomatic carrier (ASC), chronic hepatitis (CH) and liver cirrhosis (LC). Second, the serial detection of HBeAg/HBeAb system was done retrospectively in the sera from the patients who were HBsAg-positive chronic liver disease and progressed to HCC. Sera of 73 patients with HBsAg-positive HCC were tested for HBeAg and HBeAb. HCC was diagnosed histologically either by liver biopsy or autopsy, or by increased alpha-fetoprotein (AFP) levels, liver scan, CT (computed tomography) scan, and celiac angiography. The control consisted of 76 patients with ASC, 101 patients with CH and 50 patients with LC. Twenty six of 73 (36%) patients with HCC were positive for HBeAg and 25 (34%) were positive for HBeAb. Positive frequency of HBeAg in the patients with ASC, CH and LC were 29%, 48% and 50% respectively. We have done the retrospective determination of HBeAg and HBeAb in sera from 11 patients with HCC who were followed as liver cirrhosis for more than 3 years. Nine of 11 patients showed persistent HBeAg-positive state throughout their clinical course and 2 of 11 showed persistent HBeAg-positive state until about 1.5 years and 2 months before occurrence of HCC respectively. (no Refs)

44. ASSOCIATION BETWEEN HLA ANTIGENS AND HEPATOCELLULR CARCINOMA (MEETING ABSTRACT)

Karvountzis GJ, Stavropoulou C, Hadziyannis SJ, Pathouli C, Renieri N, Komninos Z
Second Department of Medicine, Athens University and National Histocompatibility Center, Athens, Greece
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Though genetic factors may play a role in the development of hepatocellular carcinoma (HCC), studies on genetic predisposition for HCC linked to the HLA antigens are rare and the results negative or controversial. In this study HLA types of 45 patients with HCC coming from a Caucasian ethnic group with a high HCC prevalence were investigated and the results were compared to those of 200 unrelated healthy controls. All patients with HCC had a firm diagnosis confirmed histologically. HBsAg and alpha1-fetoprotein (alphafp) were tested in all patients by RIA (radioimmunoassay). For HLA typing the microlymphocytotoxicity Terasaki's technique was used. One hundred antisera were used in each case for the detection of 11 HLA-A and 19 HLA-B specificities. Apparent distribution differences between patients and controls were restricted to HLA-A3, HLA-B7 and HLA-B14. These differences were statistically significant only for B7 and B14 and B14. The observed increases of A3 reached statistical significance in the group of HBsAg positive patients. The above association between particular HLA antigens (A3, B7, B14) and HCC observed in a Caucasian ethnic group, is in contrast to the negative results reported in South African Blacks and suggests that in the population studied genetic factors linked to HLA antigens are of importance in the development of HCC. (no Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

45. ALPHA-1-ANTITRYPSIN DEFICIENCY IN SOUTHERN AFRICAN HEPATOCELLULAR CARCINOMA PATIENTS. AN IMMUNOPEROXIDASE AND HISTOCHEMICAL STUDY.

Cohen C, Berson SD, Budgeon LR
Dept. Anatomic Pathology, Milton S. Hershey Medical Center, Hershey, PA, 17033
Cancer; 49(12):2537-2540 1982

An increased frequency of alpha-1-antitrypsin deficiency (AATD) has been reported in patients with hepatocellular carcinoma (HCC) in Scandinavia and England. Using a specific immunoperoxidase technique for alpha-1-antitrypsin (AAT) and periodic acid-Schiff (PAS) with and without diastase predigestion, the authors examined nonneoplastic autopsy liver tissue from 58 black southern African patients with HCC and from 54 controls. No periportal PAS-positive diastase-resistant globules containing AAT (specific for AATD) were found in liver tissue from either group. A finely granular diffuse cytoplasmic AAT staining (not removed by diastase predigestion) was present in hepatocytes in a 'checkerboard' pattern within the lobule in 33 (57%) HCC patients and in 20 (37%) controls (p less than 0.1), and was particularly prominent adjacent to tumor in 11 HCC patients. Alpha-1-antitrypsin was present in neoplastic cells in 18 of the 40 HCC examined (45%). These findings suggest no major role for AATD in the etiology of HCC in southern Africa. (Author abstract) (33 Refs)

46. IMMUNOELECTRON MICROSCOPIC STUDY ON ALPHAFETOPROTEIN SYNTHESIS.

Lin Chu M, Chang TW, Chuong CM, Lin WS
Dept. Pathology, Coll. Medicine, Natl. Taiwan Univ., Taipei, Taiwan
Taiwan I Hsueh Hui Tsa Chih; 81(2):127-134 1982

Human fetal liver and hepatoma cells were compared with respect to ultrastructural localization of alphafetoprotein (AFP) by immunoelectron microscopy. The AFP-synthesizing cell was found to be a hepatocellular carcinoma cell with the same pattern of positive distribution of immunoenzyme reaction products characteristic of AFP in the cytoplasm as those of the fetal hepatocytes. Synthesis of AFP in the tumor state appears to be the result of depression of the oncodevelopmental protein (AFP), which after depression follows the same pathway as in the fetal state. (22 Refs)

47. HISTOLOGIC GROWTH PATTERN OF HEPATOCELLULAR CARCINOMA: RELATIONSHIP TO ORCEIN(HEPATITIS B SURFACE ANTIGEN)-POSITIVE CELLS IN CANCER TISSUE.

Nakashima T, Kojiro M, Kawano Y, Shirai F, Takemoto N, Tomimatsu H, Kawasaki H, Okuda K
(c/o Okuda) First Dept. Medicine, Chiba Univ. Hosp., Chiba 280, Japan
Hum Pathol; 13(6):563-568 1982

The histologic pattern of tumor growth at tumor-nontumor boundaries was studied in 60 livers bearing hepatocellular carcinoma. Three growth patterns, arbitrarily described as 'sinusoidal,' 'replacing,' and 'encapsulated,' were distinguished. Cancer cells growing in the sinusoids between liver cell cords (sinusoidal pattern) were anaplastic; those growing in an expansile fashion and acquiring a fibrous capsule (encapsulated pattern) were most differentiated; and those growing into the cord of liver cells and replacing them (replacing pattern) were differentiated to an intermediate degree. There was certain relation between the histologic growth patterns and gross morphologic features of the tumors. Test results for 20 of the 60 cases were positive for serum hepatitis B surface antigen (HBsAg), and the livers also contained orcein-positive cells. Orcein-positive cells were frequently seen at the border between tumor and parenchyma. Cells containing HBsAg as an orcein-positive inclusion were present in cancer tissue in three cases. When serial sections were made from such areas and stained alternately with hematoxylin and eosin and orcein, it was found that these cells were hepatocytes blended with cancer cells. This phenomenon was related to the growth pattern of tumor cells. Orcein-positive cells were never found in metastatic lesions. (Author abstract) (28 Refs)

48. CLEAR CELL CARCINOMA OF LIVER: AN ULTRASTRUCTURAL STUDY AND CORRELATION WITH BIOLOGICAL BEHAVIOUR (MEETING ABSTRACT)

Wu PC, Lai CL, Lok AS
Department of Pathology, University of Hong Kong, Hong Kong, Hong Kong
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asien Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

A study of 80 Chinese patients with histologically proven hepatocellular carcinoma (HCC) and no anti-tumor treatment showed that those with clear-cell pattern (ie more than 50% of the carcinoma cells had clear cytoplasm) had a significantly better 50% survival rate compared to those with no clear cells in their tumors. To explain the better prognosis of clear-cell HCC, a light microscopic and ultrastructural study of ten consecutive cases each of clear cell HCC and non-clear HCC was performed. The clear cells contained substantial quantities of glycogen and lipid which partly replaced the usual cytoplasmic constituents. Rough endoplasmic reticulum (RER) occurred in smaller quantities and appeared in short fragments failing to form stacks in contrast to the characteristic stacks in normal mature hepatocytes. Polyribosomes and ribosomes were also diminished. Swelling of the mitochondria and hydration of cytoplasmic matrix with breaks in the mitochondrial membranes were observed in two cases. A comparison was made between these tumor cells with clear cytoplasm and the clear cells which occurred during animal experimental carcinogenesis. The abnormal accumulation probably reflects intrinsic metabolic defect in the cell and changes in the rough endoplasmic reticulum, ribosomes and mitochondria suggest that the tumor cell is not of the fast-growing type. A correlation with its more favorable outcome was attempted. (no Refs)

49. IMMUNOHISTOCHEMICAL FERRITIN IN HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT)

Cohen C, Berson SD, Shulman G, Budgeon LR
Department of Pathology, The Milton S. Hershey Medical Center of the Pennsylvania State University, Hershey, PA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Serum ferritin concentrations are elevated in 35 to 100 per cent of patients with hepatocellular carcinoma (HCC). Using an immunoperoxidase technique, we demonstrated ferritin in tumor tissue from 32 to 74 (43 per cent) black southern African patients and from 12 of 19 (63 percent) American patients with HCC. Ferritin was present in non-neoplastic liver in 38 of 65 (59 percent) African and 12 of 13 (92 per cent) American patients. Moderate to large amounts of stainable hepatic storage iron were present in 77 per cent of the African and 67 per cent of the American patients. Fifty-two of 74 (70 per cent) African patients had macronodular or mixed cirrhosis. Thus, high serum ferritin levels in patients with HCC may be due to ferritin production by the tumor or to the associated cirrhosis and/or iron overload. Other suggested but disproved mechanisms include leakage of storage ferritin from necrotic liver cells and impaired hepatic uptake of serum ferritin. The liver ferritin antibody used in our immunoperoxidase method demonstrates basic isoferritins and probably underestimates actual tumor ferritin which, in addition, consists of acidic tumor ferritin which, in addition, consists of acidic isoferritins said to be tumor-specific. (no Refs)

50. HISTOLOGIC AND SEROLOGIC EVALUATION OF HEPATOCELLULAR CARCINOMA (HCC) IN KOREA (MEETING ABSTRACT)

Chung WK, Chung KW, Sun HS, Kim BS, Hoofnagle JH, Minuk GY, Gerber MA, Thung S, Popper H
Department of Medicine, Catholic Medical Center, Seoul, Korea
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Independent needle biopsy specimens were obtained by laparoscopy from noninvolved liver and from tumor in 33 patients with HCC and from nontumorous liver in 12 patients in whom HCC developed 1-13 years later. Routine microscopy revealed in the surrounding liver ground-glass hepatocytes 10 times, dysplastic hepatocytes 22 times, adenomatous nodules 21 times. In toto, potential precursor lesions were found in 75% of cases in the cancer stage and in 58% before. Shikata orcein stains for HBsAg were positive in 33%. These observations were elaborated by immunoperoxidase study for HBsAg, HBcAg and alpha-fetoprotein. Chronic active hepatitis (CAH) was found only 4 times while the tumor was present, and 9 times before the tumor was found, suggesting common regression of CAH at the cancer stage. Serologically in 83% HBsAg was found and in all remaining cases anti-HBc, suggesting association with hepatitis B infection in all cases, of which 38% also had serum HBeAg but only 3% had DNA polymerase. HCC in Korea is almost always associated with HB infection, has the characteristic cytologic precursor lesions, but usually little activity of the hepatitic process in the cancer stage, while viral replication appears to persist sometimes. (no Refs)

51. ISOLATION AND TRANSPLANTATION OF PRECURSORS IN HEPATOCARCINOGENESIS (MEETING ABSTRACT)

Miller SB, Pretlow TP, Pretlow TG
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71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The role of cells frequently termed putative preneoplastic cells in hepatocarcinogenesis is still unclear. Two types of cells widely regarded as possible precursors of hepatomas are the 'enzyme-altered hepatocyte' and the 'oval cell'. Both of these cells have histochemically demonstrable gamma-glutamyl transpeptidase (GGT). We have attempted to isolate each of these cell types free of the other to test their biologic potentials. Half a billion liver cells were purified by velocity sedimentation in the Dupont-Sorvall TZ-28 reorienting zonal rotor. When purified preparations of 98.8 per cent hepatocytes were injected into the mesenteric veins of syngeneic rats fed a diet with 0.02 per cent acetylaminofluorene and subjected to partial hepatectomy, all rats developed foci of cells with GGT in their livers in 10 days. Type II cells, small cells with intense GGT, were purified in an isokinetic gradient followed by free-flow electrophoresis. Preparations with 37.2 per cent type II cells and only 1.6 per cent hepatocytes were injected into syngeneic hosts prepared as described above. Recipients of type II cells also developed hepatic foci with GGT within 10 days. Both enzyme-altered hepatocytes and type II cells make up part of what previously has been referred to as 'liver colony-forming units'. (no Refs)

52. HISTOCHEMICAL AND ELECTRON SPIN RESONANCE STUDY OF SERUM METALLOPROTEINS IN DAB HEPATOMA.

Kawasaki H, Nakashima T, Tanaka H, Terada S, Kimoto E
1st Dept. Pathology, Kurume Univ. Sch. Medicine, Kurume 830, Japan
Acta Histochem Cytochem; 15(1/2):270-276 1982

Immunohistochemical demonstration of hepatic ceruloplasmin and transferrin was studied and the characterization of the states of copper and iron bound to these proteins was investigated by electron spin resonance measurements in p-dimethylaminoazobenzene (DAB)-induced hepatomas of rats. Every hepatic tissue from DAB hepatoma-bearing rats exhibited very high fluorescence for both of the investigted proteins. DAB hepatoma showed a profound signal which was ascribed to the perpendicular component of cupric ions. Normal livers did not show the copper signal at all. (29 Refs)

53. IRON EXCLUSION FROM AFLATOXIN B1-INDUCED HEPATOCELLULAR CARCINOMA IN RATS (MEETING ABSTRACT)

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Toxicologist; 2(1):98 1982

Previous studies have shown that partial hepatectomy followed by an hepatic carcinogen induces foci which exclude iron. The purpose of this experiment was to test the hypothesis that altered foci induced by Aflatoxin B1 (AFB1) are resistant to iron accumulation without any other manipulation, ie, partial hepatectomy or altered diet. Male weanling Sprague-Dawley rats received 50 ug/rat/day of AFB1 in DMSO (dimethyl sulfoxide) by stomach intubation to a total dose of 1.10 mg AFB1/rat. Age- and sex-matched controls received similar volumes of DMSO. Eighteen months after administration of the last dose of the toxin half the animals in each group received iron dextran intraperitoneally (125 mg/kg/day) for three days and the other half of each group received no iron treatment. Preserved liver sections stained with hematoxylin and eosin (H and E) indicated the presence of mixed cell hepatocellular carcinomas in AFB1-treated rats. No hepatic lesions were observed in control rats. Iron staining by the Gomori method showed exclusion of iron dextran from the tumor sites. Areas of normal tissue were deeply stained for iron, both in Kupffer cells and hepatocytes. (no Refs)

54. THE LIGHT AND ELECTRON MICROSCOPIC EVALUATION OF CHOLANGIOCELLULAR NEOPLASMS IN THE RAT LIVER FOLLOWING CHRONIC AROCLOR 1260 EXPOSURE (MEETING ABSTRACT)

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Toxicologist; 2(1):100 1982

Simple cholangioma (C), cystic C, cholangiofibrosis (CF), and mixed hepatocholangiocellular carcinoma (MHC) were observed in the livers of 93 Sprague-Dawley rats fed Aroclor (100 ppm for 16 months followed by 50 ppm for 8 months) at an incidence of 38, 7, 9, and 26%, respectively. C(8%), CF(4%), and MHC(0%) occurred in 81 rats fed a control diet. The cholangiocyte, a pale-staining epithelial cell in the bile duct of the portal triad, possessed the following subcellular morphology; A clefted nucleus; few cisternae of rough endoplasmic reticulum (ER), tubules of smooth ER, Golgi complexes, and mitochondria; many ribosomes, cytoplasmic filaments, and apical surface microvilli; lateral junctions and membrane undulations; and a smooth basal surface resting on a basal lamina. A cholangiocyte subcellular morphology was observed in C cells. CF possessed cuboidal to columnar simple and pseudostratified epithelium, numerous mitoses, and few PAS-positive goblet cells. Cells of CF demonstrated features of cholangiocytes; differences included a prominent nucleolus, increased organelles, and numerous desmosomes. In the MHC, the ductal cell was PAS negative and the features varied. Some cells possessed a cholangiocyte morphology. Other cells contained subcellular features typical of hepatocytes: A round nucleus, prominent nucleolus, abundant rough ER, lamellar smooth ER, lysosomes, smooth intercellular surfaces, absent basal lamina, and canaliculi between ductal cells and hepatocytes. Aroclor 1260 induces lesions of both hepatocellular and cholangiocyte differentiation. (1 Ref)

55. THE SIGNIFICANCE OF CHOLANGIOFIBROSIS AS A 'PRENEOPLASTIC LESION' (MEETING ABSTRACT)

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Toxicologist; 2(1):100 1982

The histogenesis of carcinoma of liver having an adenomatous or ductal pattern is uncertain. Many consider that such tumors arise from bile ducts and is preceded by cholangiofibrosis; others consider that they are histological variants of hepatocellular carcinoma. The changes produced in the liver of rats by 3'Methyl-4-diaminoazobenzene (3'MeDAB) and by coumarin are compared. 3'MeDAB administration led to extensive oval cell proliferation and then to cholangiofibrosis. This was followed by hepatic nodules with variable enzyme patterns and later, trabecular and adenomatous or duct carcinoma. Coumarin induced cholangiofibrosis in which four distinct stages could be recognized. No altered foci, areas or nodules were seen, and no hepatocellular tumors developed. The ultrastructure appearance of cholangiofibrosis was compared with that of adenomatous areas of carcinoma. Cells forming the lining epithelium in both were similar. Carcinomas with ductal or adenomatous pattern were deep within unequivocal hepatocellular carcinoma and it is considered that they represent variants of such tumors. Occasionally ductal tumors appeared to arise within cholangiofibrosis. Possibly proliferating ducts exposed to a carcinogen may be susceptible to neoplastic change. It is concluded that most of tumors, induced by 3'MeDAB, even those are variants of hepatocellular carcinoma. (no Refs)

56. AN EVALUATION OF DIMETHYLNITROSAMINE (DMN) - INDUCED HEPATOCELLULAR ALTERATIONS IN THE NEWBORN MOUSE MODEL USING HISTOCHEMICAL AND HISTOENZYMATIC MARKERS (MEETING ABSTRACT)

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Toxicologist; 2(1):99 1982

Newborn Swiss mice were dosed IP with 25 ug of DMN or saline, and at weaning placed on drinking water containing 0.05% phenobarbital (PB), a known promoter of hepatocellular carcinomas, or water alone, Preneoplastic foci (F) and hyperplastic nodules (HN) were identified histologically by two markers; resistance to exogenous iron accumulation and an increase in gamma-glutamyl transpeptidase (GGT) activity. F were distinguished from HN by size and by compression of the surrounding parenchymal cells. In the DMN and PB group, livers of affected male mice at 6,8,12 and 16 wk exhibited 6,10,17 and 12 iron resistant F/cm2 and 10,13,9 and 9 GGT-F/cm2, respectively. At these same time periods iron resistant-F in affected females ranged from 5-11 F/cm2, while GGT-F ranged from 9-16 F/cm2. Iron resistant HN were first observed in male mice at 8 wk; however, GGT-HN were not noted until 12 wk. By 12 and 16 wk affected males had 6 and 4 iron resistant HN/cm2 while affected females had 4 and 6, respectively. At these same time points, males had 6 and 3 GGT-HN/cm2 while females only displayed GGT-HN at 16 wk (6 HN/cm(2)). The DMN alone group contained an average of 4 F/cm2 (iron resistant or GGT) while no HN were noted in any group except the DMN and PB. Lung nodules were apparent as early as 6 wk in both sexes of the DMN alone group and at 12 wk in the DMN and PB group. (no Refs)

57. LIVER CELL DYSPLASIA IN ASSOCIATION WITH HEPATOCELLULAR CARCINOMA AND CIRRHOSIS IN HONG KONG (MEETING ABSTRACT)

Wu PC, Ho JC, Mak TK, Lai CL, Gibson JB
Department of Pathology, University of Hong Kong, Hong Kong, Hong Kong
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Necropsy and biopsy materials from Chinese patients with cirrhosis, hepatocellular carcinoma (HCC) or HCC associated with cirrhosis admitted into Queen Mary Hospital, Hong Kong were studied. Liver cell dysplasia was found in 337 of 558 post-mortem cases of cirrhosis and in 203 of 309 cases of HCC. It was significantly more frequently identified in livers showing both cirrhosis and HCC than in livers showing HCC alone or cirrhosis only. Applying Bayes' theorem, the risk facing dysplasia-positive Chinese males in developing HCC was calculated. For Chinese male non-cirrhotics with liver cell dysplasia at necropsy, compared with male non-cirrhotics without dysplasia, the approximate risk factor for HCC is 13:1, whereas the male cirrhotics with liver cell dysplasia, compared with male cirrhotics without dysplasia, the risk for HCC is approximately 2:1. A significant correlation was also found between liver cell dysplasia and the presence of hepatitis B surface antigen (HBsAg) in the livers. In the presence of dysplasia, the risk for HCC is increased two-fold in males who are also HBsAg-positive. Therefore the presence of liver cell dysplasia in both cirrhotic and non-cirrhotic Chinese males carries a significantly higher risk of developing HCC, and the risk is even greater in those who are HBsAg-positive. (no Refs)

58. CHANGES OF HEPATOCYTE PROLIFERATION IN MOUSE LIVER AND ADENOMATOUS NODULES DURING CCL4-INDUCED CARCINOGENESIS.

Faktor VM, Poltoranina VS, Uryvaeva IV
Lab. Cytology, N. K. Kol'tsov Inst. Biology Development, Moscow, USSR
Biull Eksp Biol Med; 93(4):79-82 1982

The effect of CCl4-induced carcinogenesis on hepatocyte proliferation was studied in SWR mice. Development of liver necrosis and foci of nodular proliferation was associated with marked decrease of the ploidy and the increase of the incidence of chromosome aberrations. These findings indicate that the early stages of liver carcinogenesis are characterized by the impairment of the mechanism of mitotic polyploidization. (13 Refs) (In RUS)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

59. ADP-RIBOSYLTRANSFERASE ACTIVITY IN CULTURED HEPATOCYTES. INTERACTIONS WITH DNA REPAIR.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC
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J Biol Chem; 257(10):5528-5535 1982

A rapid increase in ADP-ribosyltransferase activity was observed when freshly isolated hepatocytes derived from adult rats were established in primary monolayer culture. (ADP-ribose)n-degrading activity remained constant over a period of 48 hr of culture. Inhibition of ADP-ribosyltransferase activity with pyridine derivatives, 3-aminobenzamide, theophylline, or thymidine, was accompanied by an enhanced DNA repair synthesis in response to the direct-acting carcinogen, methyl methanesulfonate, or UV irradiation. Three aminobenzamides differing only in the position of the amino group exhibited the same structure-activity relationship in regard to their action on DNA repair synthesis and ADP-ribosyltransferase. Spermine treatment of hepatocytes apparently had an inverse effect on both these cellular functions. The removal of DNA strand breaks following methyl methanesulfonate treatment was accelerated by inhibitors of ADP-ribosyltransferase. The results suggest that ADP-ribosylation interacts with late stages in the process of DNA repair. This interaction apparently is dependent on the nature of damage imposed on chromatin since repair synthesis in response to a number of carcinogens is unaffected by inhibitors of ADP-ribosyltransferase. (Author abstract) (52 Refs)

60. ETHIONINE INHIBITS IN VIVO METHYLATION OF NUCLEAR PROTEINS.

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Carcinogenesis; 3(4):431-434 1982

Nuclear protein methylation was studied in regenerating rat liver by giving [methyl-3H]methionine 45 hr after partial hepatectomy. Ethionine, a liver carcinogen, has been shown to alter the methylation patterns in a basic protein (histone) fraction, as well as an acidic protein (non-histone) fraction present in a 0.25 N HCl nuclear extraction. The proteins present in the 0.25 N HCl extraction were separated by chromatography using Bio-Rex 70 cation exchange column. Polyacrylamide gel electrophoresis and total amino acid analysis showed the first protein fraction contained acidic large mol wt non-histone proteins, while the second fraction contained basic small mol wt histone proteins. Both fractions were then hydrolyzed, and the amino acids chromatographed on an Aminex A-5 cation exchange column. The histones were found to contain epsilon-N-mono, di and trimethyllysine derivatives; whereas the non-histone fraction contained these lysine derivatives and an additional basic amino acid identified as NG,NG-dimethylarginine. Ethionine (0.5 mg/g body wt) was found to inhibit in vivo methylation of lysine to form epsilon-N-mono, di and trimethyllysine, 46, 52 and 68%, respectively. The formation of NG,NG-dimethylarginine was inhibited by 85%. Ethylation of these proteins was also studied by giving [ethyl-3H]ethionine. After hydrolysis, the non-histones were found to contain a labeled lysine and arginine derivative, but in the histone fraction only labeled lysine was found. (Author abstract) (21 Refs)

61. QUANTITATIVE ASSESSMENT OF CARCINOGEN-MODIFIED DNA IN SPECIFIC LIVER CELL POPULATIONS FOLLOWING A SINGLE DOSE N-2-ACETYLAMINOFLUORENE (AAF) OR ITS N-HYDROXY DERIVATIVE (N-OH-AAF) (MEETING ABSTRACT)

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Toxicologist; 2(1):103 1982

AAF-induced hepatocarcinogenesis appears to be targeted to parenchymal cells (PC). Our objective was to determine whether or not there is preferential binding of carcinogen (C) residues to the DNA of these target cells and, if so, the possible basis for the selectivity. AAF and its N-hydroxy derivative (N-hydroxyl-N-2-acetylaminofluorene), the first product in the metabolic activation of AAF, were employed for these studies. Male Sprague-Dawley rats weighing 200-250 g were injected, ip, with (ring-3H)AAF or (ring3H)-N-OH-AAF. Animals were sacrificed at either the time of peak binding of C to DNA, 2 hr or 18 post-injection, when N-OH-AAF or AAF, respectively, were used, and at 3 days after maximum binding. PC and nonparenchymal (NPC) cells were isolated by centrifugal elutriation. Following AAF administration, the u moles of adducts formed/mg DNA of PC was 2.7 times that of the NPC. When N-OH-AAF was employed, equal amounts of adducts were found associated with DNA of PC and NPC. By 3 days after the period of maximum DNA binding 50-59% of the adducts initially present remained in the DNA of both cell types following administration of either AAF or N-OH-AAF. These results suggest that AAF preferentially damages DNA of PC due to an increased capacity of these cells to carry out the N-hydroxylation of AAF. (no Refs)

62. DNA ALKYLATION DURING CHRONIC DMN EXPOSURE OF MALE AND FEMALE C3H MICE (MEETING ABSTRACT)

Lindamood C, Billings KC, Bedell MA, Swenberg JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC
Toxicologist; 2(1):101 1982

The hepatocarcinogenicity of dimethylnitrosamine (DMN) is sex-dependent in C3H mice following chronic oral exposure. DMN causes predominently hepatomas in males and capillary endotheliomas in females. The purpose of this study was to assess the role of the promutagenic DNA lesion O6-methylguanine (O6MG), in the cellular specificity of DMN's carcinogenicity in C3H mice. Male and female mice were given 0 or 10 ppm DMN ad libitum in the drinking $H2O$ for 2, 4 or 16 days. The DMN dosage varied from 1.74-2.14 mg/kg/day among the treatment groups. Livers were perfused in situ with collagenase and hepatocytes and nonparenchymal cells. (NPCs) separated by differential centrifugation. DNA was isolated by hydroxyapatite chromatography and purine bases separated by HPLC (high performance liquid chromatography) and quantitated from UV-absorbing and fluorescing peaks. Concentrations of 7-methylguanine (7-MG) in the 2 liver cell populations of both sexes increased between 2 and 4 days of exposure and remained relatively constant thereafter. NPCs of both sexes accumulated O6MG over the time course of DMN administration, such that increasing O6MG/MG ratios were observed. Male and female hepatocytes demonstrated increased removel of O6MG after exposure to DMN. Concentrations of hepatocellular O6MG in both sexes were 5 to 7 fold less at 16 days than at 4 days, resulting in decreased O6/7MG ratios. (1 Ref)

63. DAMAGE TO RAT LIVER DNA FROM IN VIVO EXPOSURE TO MONOCROTALINE, A PYRROLIZIDINE ALKALOID (MEETING ABSTRACT)

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Toxicologist; 2(1):102 1982

Pyrrolizidine alkaloids (PAs) are known to damage DNA in vitro, to be hepatocarcinogens in animal models, and have been linked to an increased incidence of hepatic carcinoma among South African Bantus. We have employed alkaline elution to detect and characterize DNA damage resulting from in vivo exposure of male Sprague-Dawley rats (150-280g) to single intraperitoneal doses of the PA, monocrotaline. Hepatic nuclei were isolated, and served as the source of DNA in all experiments. No evidence of single-strand breaks, as would be indicated by an increased rate of DNA elution from the filter as compared to controls, was detected at either 4 or 8 hr after doses of up to 120mg/kg of monocrotaline. As monocrotaline may be bioactivated to bifunctional alkylating agents, experiments were conducted to detect DNA cross-links. In contrast to the results of the single-strand break experiments, evidence for DNA cross-links was observed at doses as low as 5mg/kg, 4 hr after administration of the PA. DNA cross-linking was detected by an apparent decrease in the number of x-ray induced single strand breaks, and consequently a decreased rate of DNA elution from the filter as compared to controls, when nuclei from both groups were x-irradiated. (no Refs)

64. STUDIES ON PARTICULATE AND SOLUBLE FORMS OF AMINOACYL-TRNA SYNTHETASES FROM RAT LIVER AND HEPATOMAS (MEETING ABSTRACT)

Del Monte U, Neri Cini G, Capaccioli S, Caldini R, Chevanne M, Perego R
University of Milan, Milan, Italy
Med Biol Environ; 9(1):375 1981

The aminoacyl-tRNA synthetases of the postmicrosomal supernatant fraction of rat hepatomas were characterized by their activity and sedimentation properties. The synthetases of hepatomas were compared with those of normal liver in terms of these parameters. The relative proportions of synthetase activities in soluble and in particulate fractions were such as to suggest that enzyme complexes are more abundant and/or more stable in hepatomas than in normal liver. (no Refs)

65. SEQUENTIAL 2-ACETYLAMINOFLUORENE-PHENOBARBITAL EXPOSURE INDUCES A CYTOSOLIC ALDEHYDE DEHYDROGENASE DURING RAT HEPATOCARCINOGENESIS.

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Carcinogenesis; 3(5):533-538 1982

A significant change in hepatic aldehyde dehydrogenase activity has been observed in normal Sprague-Dawley rat liver during the promotion phase of hepatocarcinogenesis induced by brief feeding of 2-acetylaminofluorene (2-AAF) followed by tumor promotion using dietary phenobarbital (PB) exposure. Animals receiving only 2-AAF or PB do not possess this new aldehyde dehydrogenase activity. The phenotype is characterized by the appearance of a new cytosolic isozyme kinetically, electrophoretically and immunochemically distinct from the normal liver aldehyde dehydrogenase isozymes and from aldehyde dehydrogenases inducible in 2-AAF-induced hepatomas. The new isozyme is NAD-dependent, disulfiram-sensitive and cross-reacts with antiserum to a normal liver aldehyde dehydrogenase inducible in several lines of rats by PB. However, the population of animals used in this study has been shown previously to be non-responsive to aldehyde dehydrogenase induction by dietary PB. Since no animals receiving only PB express this new isozyme, the carcinogen must play a significant role in its induction. Moreover, that not all animals receiving carcinogen and promoter possess the phenotype suggests this carcinogen/promoter interaction has a genetic basis. (Author abstract) (19 Refs)

66. GLUTATHIONE S-TRANSFERASE IN HUMAN HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT)

Sherman M, Titmuss S, Kew MC, Kirsch RE
MRC Liver Research Group, University of Cape Town, Cape Town, South Africa
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

The human hepatic glutathione S-transferase (GSH-T) consist of 3 groups. The basic group (pI 7.5-9) are all immunologically identical. GSH-T mu has a pI of 6-6.5. The most acidic GSH-T's (pI 4.5-5.4) are reported to react with antibodies to the basic transferases. The acidic GSH-T's are not present in all specimens of liver examined. In hepatocellular carcinoma (HCC) GSH-T enzyme activity and immunoreactivity are reduced. It is not known to what extent the individual transferases are affected. Two specimens of normal liver and four HCC's were obtained within 12 hours of death. Cytosol was prepared and subjected to isoelectric focusing in a sucrose density gradient. GSH-T activity was measured using 1-chloro-2,4-dinitrobenzene as substrate. Immunoreactivity was measured by radioimmunoassay using an antibody to the basic GSH-T's. Enzyme specific activity in normal liver cytosol was 0.69umol/min/mg protein, and in tumor cytosol was 0.03 (0.01-0.10) umol/min/mg. The basic transferases were present in both specimens of normal liver, and the acidic GSH-T was present in one specimen. GSH-T mu was not detectable in either specimen. Immunoreactivity was limited to the basic GSH-T's. In all four tumors the acidic transferases were present in varying ratios. These were not immunoreactive. In one tumor specimen the basic GSH-T enzyme activity was undetectable and the peak of immunoreactivity was only 80 ng/ml. In the other three tumors the basic GSH-T's were present, but reduced. Immunoreactivity was confined to the basic GSH-T's and there was good correspondence between the enzyme and immunoreactive profiles. (no Refs)

67. EFFECTS OF ALPHA-NAPHTHYLISOTHIOCYANATE, LITHOCHOLIC ACID AND SELECTED HEPATOCARCINOGENS ON EPOXIDE HYDROLASE, DT-DIAPHORASE AND SERUM INDICATORS OF CHOLESTASIS (MEETING ABSTRACT)

Thompson MB, Dent JG, Graichen ME, Neptun DA, Scortichini BH, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):101 1982

The classic cholestatic agent alpha-naphthylisothiocyanate (ANIT) elevates the hepatic preneoplastic marker epoxide hydrolase (EH). Abilities of 3 hepatocarcinogens and 2 cholestatic agents to produce cholestasis and enhance hepatic EH activity were compared. Hepatocarcinogens 2-acetylaminofluorene (AAF) at 100 ppm or 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) at 600 ppm in the diets or diethylnitrosamine (DEN) at 40 ppm in the drinking water were given to male, Fischer-344 rats (200-270 g). The cholestatic agents ANIT at 1000 ppm or lithocholic acid (LA) at 10,000 ppm in the diets were fed to comparable groups. Concentrations of total bile acids (BA), total cholesterol (CH) and total bilirubin (BIL) and the activity of gamma-glutamyltranspeptidase (GGT) were measured in serum at 2, 4 and 6 weeks. Activities of hepatic microsomal epoxide hydrolase (EH) and cytosolic DT-diaphorase (DTD) were determined. Serum BA concentrations were increased by all treatments. ANIT treatments produced the greatest increases. AAF an 3'-MeDAB caused intermediate increases and DEN and LA the smallest. CH and BIL concentrations and activities of GGT and DTD were only increased by treatment with ANIT. EH was increased by all treatments except LA. At 2 and 6 weeks animals exposed to AAF, DEN and 3'-MeDAB had a direct correlation between serum BA and EH activities. (no Refs)

68. EFFECT OF HEPATOCYTE PROLIFERATION AND NEOPLASTIC TRANSFORMATION ON ALPHA-FETOPROTEIN (AFP) AND ALBUMIN (ALB) PRODUCTION PER CELL. INFLUENCE OF CELL SPECIALIZATION AND CELL SIZE.

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Oncodev Biol Med; 3(1):49-63 1982

Hepatocytes were isolated from 2-day regenerating livers of 21-day- and 12-wk-old rats, and the percentage of cells specialized in AFP and ALB production was evaluated using the reverse hemolytic plaque assay. In comparison to the data obtained with hepatocytes from non regenerating livers, the percentage of ALB producers was not significantly modified during the regenerating process; the percentage of AFP producers at 23 days of age went from a non detectable level to 5% while at 12 wk it remained at an extremely low value. Double identification of secreting hepatocytes further revealed that the re-occurring AFP producers were recruited among those already producing ALB. The isolated hepatocytes were also fractionated according to size by velocity sedimentation at 1 x g and the actual production rate of AFP and ALB was determined on a per cell or a per mg protein basis. Again, regeneration process did not alter the ALB production rate, whereas AFP became detectable only with hepatocytes from 23-day-old rats. The same approach was used to evaluate the relationship between AFP/ALB specialization versus cell size for Morris 7777 and 7795 and Novikoff hepatoma cells. The results showed that on a per mg basis, after correction for the percentage of specialized cells, Morris 7777 cells produced AFP at a rate comparable to that of the normal neonatal hepatocytes. Both Morris 7777 and 7795 hepatoma cells produced ALB at a low rate. Novikoff hepatoma cells produced no detectable amount of the two exportable proteins. The analysis by velocity sedimentation at 1 x g also revealed that the three hepatoma cell lines were essentially identical in size. They were found to be smaller than neonatal hepatocytes but comparable in size to hepatic epithelial cells that can be isolated from normal rats and propagated in culture. These results are discussed in terms of proposals suggesting that hepatic epithelial cells may correspond to precursors or stem cells of hepatocytes and to target cells during chemical hepatocarcinogenesis. (Author abstract) (56 Refs)

69. ALPHA-FETOPROTEIN SYNTHESIS DURING EARLY STAGES OF HEPATOCARCINOGENESIS IN MICE WITH DIFFERENT SENSITIVITY TO ORTHO-AMINOAZOTOLUENE.

Serova IA, Kaledin VI, Kostyrev OA, Grantenko EV
Inst. Cytology and Genetics, Novosibirsk, USSR
Dokl Akad Nauk SSSR; 263(5):1245-1249 1982

Alpha-fetoprotein (AFP) synthesis during ortho-aminoazotoluene (OAT) induced liver carcinogenesis was studied in OAT-sensitive DD/He, DBA/2J, CBA/LacSto, and A/He mice and in OAT-resistant CC57BR/Mv and BALB/cLacSto mice. The ip or sc administration of OAT produced marked necrotic changes in the liver of sensitive mice. Resistant mice and sensitive CBA mice did not show morphological changes in the liver tissue. Both sensitive and resistant mice showed the first peak of AFP on day 4 after OAT administration. The resistant mice showed normalization of AFP blood levels, while the sensitive mice developed the second increase of AFP level. (10 Refs) (In RUS)

70. ALPHA-FETOPROTEIN DYNAMICS DURING ETHIONINE-INDUCED HEPATOCARCINOGENESIS IN RAT.

Miyazaki M, Wahid S, Matsuura K, Watanabe A
Div. Pathology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Res Exp Med (Berl); 180(2):155-159 1982

The dynamics of alpha-fetoprotein (AFP) during hepatocarcinogenesis induced by DL-ethionine (ET) was studied in adult female Sprague-Dawley rats. Rats were fed a powdered basic diet which contained 0.25% ET throughout the more than 7 mo of the experiment. AFP in the serum and in liver tissue was determined by a radioimmunoassay using the double antibody method. Serum AFP in ET-fed rats reached a max of 1,500 nanog (ng)/ml in wk 6, with subsequent gradual decline to 500 ng/ml between wk 10 and 14. Serum AFP levels then rose to 1,300 ng/ml in wk 22, by which time well-differentiated hepatocellular carcinomas had developed, and then declined markedly. AFP content (ng/g tissue) in ET-induced hepatoma (610) was slightly lower than that in adjacent non-tumorous portions of liver (687). These observations indicate that the hepatocellular carcinoma induced by ethionine does not produce high concentrations of AFP. (13 Refs)

71. ON THE LIKELY MECHANISMS BY WHICH CARCINOGENS INDUCED ADRIAMYCIN RESISTANCE IN RAT HEPATOCYTES (MEETING ABSTRACT)

Carr BI, Langley DB
Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, 91010
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Administration of the hepatocarcinogen 2-acetylaminofluorene (AFF) to rats induces a resistance in their hepatocytes to doses of adriamycin (Ad) that are cytocidal to normal hepatocytes after incubation in vitro in primary monolayer culture. To investigate the mechanism of this carcinogen-induced resistance, sensitive (normal) and resistant (2-AAF altered) hepatocytes were incubated with Ad 1.8 x 10-5M for periods up to 24 hrs. No differences were observed in the cellular uptake, efflux, DNA-binding, DNA nicks, or inactive Ad aglycone metabolites between sensitive and resistant cells. However, only 50% of the fluorescing material was organic extractable. Examination of the aqueous non-extractable material revealed that this comprised 13% of the total cellular fluorescence in the sensitive cells and 34% in the resistant cells. It contained mainly highly polar metabolites, presumably water-soluble conjugates. Administration of Ad mg/kg iv to normal or 2-AAF treated rats resulted in similar concentrations of Ad and % fluorescence in the non-toxic aglycone metabolites. No Ad-OH was observed. (1 Ref)

72. A POSSIBLE ROLE OF HORMONES ON HEPATOCYTE AND HEPATOMA CELL PROLIFERATION (MEETING ABSTRACT)

Coetzee ML, Ove P
Department of Anatomy and Cell Biology, University of Pittsburgh, Pittsburgh, PA
Anat Rec; 202(3):33A 1982

Evidence is provided that proliferation of hepatocytes and transplantable Morris hepatoma 7777 might to some extent be regulated by triiodothyronine (T3), the adrenals and/or a specific serum protein, the levels of which are correlated with serum T3 levels. We have reported elevated levels of the serum protein following partial hepatectomy and a single injection of T3 and both are correlated with increased hepatic DNA synthesis. Both the cell proliferation of hepatoma 7777 and the circulating levels of the serum protein were decreased in thyroidectomized rats. When serum protein levels were elevated as a result of removal of 70% of the liver or a single injection T3, prior to transplant, accelerated hepatoma growth was observed. A tumor implanted into the back rather than in the thigh can be easily excised after 10 days with little injury to the animal. When this original transplant was surgically removed, serum protein levels rise rapidly and remain elevated for some time. A 2nd hepatoma transplant now grows at an accelerated rate. Both serum T3 and thyroxine (T4) levels are extremely low following thyroidectomy, but T3 levels are dramatically increased in hepatoma-bearing animals, while T4 levels remain constant. Adrenalectomy, performed 24 or 48 hr prior to partial hepatectomy, enhanced the response of increased DNA synthesis. On the other hand, dexamethasone, injected 48 hr prior to partial hepatectomy, completely inhibited the dramatic burst of hepatic DNA synthesis that usually occurs 20 hr post-operatively. (1 Ref)

REVIEWS AND OTHER RELATED STUDIES

73. LIVER TUMOURS: NEW ASPECTS.

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Hepatogastroenterology; 28(1):1-5 1981

The frequency, etiology, pathogenesis, diagnosis, treatment, and prevention of primary liver carcinoma (PLC) are discussed. PLC occurs 4x more often in males than in females and is usually preceded by chronic hepatic disease. Genetic disposition to PLC has been observed. Exogenous environmental influences on PLC are considered. Serological and morphological diagnoses of PLC are described. The only curative therapy for PLC is radical surgical removal of the tumor-involved lobe of the liver. Palliative therapy with chemotherapy or interferon has been attempted. (44 Refs)

74. VINYL CHLORIDE-INDUCED HEPATIC LESIONS IN MAN AND RODENTS. A COMPARISON.

Popper H, Maltoni C, Selikoff IJ
Stratton Lab. for the Study of Liver Disease, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY
Liver; 1(1):7-20 1981

Parallel sequences in the liver of man, rats, and mice exposed to vinyl chloride (VC) were compared to review pathologic features induced, to document similarities in evolution from precursor lesions to malignant states, and to compare the evolution with that caused by other carcinogenic agents. Available for study were 19 human cases of angiosarcoma and precursor lesions following exposure to VC, previously reported, plus 5 additional angiosarcomas (autopsy) and 16 precursor lesions (biopsy material). Rats and mice had been exposed to VC in inhalation chambers. In man, the number of sinusoidal cells conspicuously increased and they almost filled the spaces between the enlarged hepatocytes. In rodents, the variety of sinusoidal cells was less conspicuous and fewer macrophages were found, but lining cells with large polychromatic nuclei similarly predominated. In man and rodents, progression of the sinusoidal dilatation associated with proliferation of the hepatocytes and sinusoidal cells loosened the parenchymal architecture. Nodules consisting of angiosarcoma cells were noted in man and rodents. Most consisted of spindle-shaped cells, in part in vascular spaces which, however, in part were also lined by nontumorous endothelial cells. In addition, in man, nodules consisted of large polyhedral sarcoma cells with abundant eosinophilic cytoplasm. The center of these nodules usually exhibited hemorrhagic necrosis and these cells then lined bloody cysts. The demonstrated similarity of the evolution in man and rodent strongly supports the extrapolation of observations from experimental animals to man. (58 Refs)

75. VIRAL HEPATITIS. 1981 INTERNATIONAL SYMPOSIUM.

Szmuness W, Alter HJ, Maynard JE

Lab. Epidemiology, Lindsley F. Kimball Res. Inst., New York Blood Center, New York, NY

Viral Hepatitis. 1981 International Symposium. Philadelphia, The Franklin Institute Press, 843 pp., 1982.

Previously unpublished reports concerning viral hepatitis were presented and discussed. Topics ranged from molecular biology to vaccine development, from hepatitis virus culture to the treatment of clinical disease, from hepatoma in the woodchuck to the association of hepatitis B virus (HBV) infection with hepatocellular carcinoma in man. New insights into the molecular anatomy of hepatitis A and B viruses were presented and the in vitro propagation of whole virus or virus-related proteins was described. DNA viruses termed 'hepadna' include human HBV and related viruses found in the woodchuck, ground squirrel, and Pekin duck. The high occurrence of hepatocellular carcinoma among animals infected with HBV-like viruses provided strong virologic support for the epidemiologic data that suggests a causal relationship between HBV infection and the development of human hepatocellular carcinoma. The epidemiology, diagnosis, pathogenesis, and chronic sequelae of hepatitis B and the evolving clinical spectrum of non-A, non-B hepatitis were discussed. Passive and active immunization programs in Australia, Japan, England, Holland, Senegal, and the United States were reported. Overall, the subunit vaccine was safe, highly immunogenic, and almost completely protective among persons who responded with development of anti-surface antibody. Abstracts and summaries of 14 workshops are presented. Unresolved issues included measures to prevent intrahospital transmission of HBV, reduction of posttransfusion hepatitis, use of corticosteroids for treatment of chronic hepatitis, and the use of hepatitis B immunoglobulin in the prevention of type B hepatitis. (1302 Refs)

76. TRENDS IN DEATH RATES FROM PRIMARY HEPATOCELLULAR CARCINOMA (HCC) (MEETING ABSTRACT)

Sandler RS, Sandler DP

Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

32nd Annual Meeting of the American Association for the Study of Liver Diseases, November 5-8, 1981, Chicago, Illinois. American Association for the Study of Liver Diseases 97 pp., 1981.

Death rates from HCC were examined by age, sex, race and geographic region using US Vital Statistics data in order to determine recent trends. Mortality from alcoholic cirrhosis and incidence of hepatitis B infection were also studied. Age-adjusted death rates from HCC for non-whites (NW) of both sexes were approximately twice those for whites (W) with rates for males about twice those for females in all time period studies. The age-adjusted death rate for NW male was 11.4/100,000 in 1975 but only 4.79 for W males. For females, the rates were 3.58 and 2.16 for NW and W respectively. Liver cancer mortality showed little change between 1960 and 1975 except among NW males for whom rates have increased, especially for those over age 60. The age-specific death rate for NW males aged 60-69 rose from an average of 10.8/100,000 between 1958 and 1962 to 14.6 between 1971 and 1975. For NW males aged 70-79 the average rate rose from 8.9 to 15.8. HCC mortality was paralleled by mortality from alcoholic cirrhosis which in 1970 was also twice as frequent among NW than W males and which doubled for NW males from 1960 to 1970. Interesting regional differences were seen. Rates from 1974-1976 for W males in the South Central and South Atlantic regions were higher than the overall rate for US W males, while rates for NW males in the same regions were significantly lower than the overall NW rate. Cirrhosis mortality for NW males was also lower in the southern regions but W rates were not higher. Although hepatitis B incidence among NW is twice that for W, it is difficult to evaluate time trends. Geographic patterns of hepatitis B do not correspond with HCC mortality. (no Refs)

77. EPIDEMIOLOGY, EARLY DIAGNOSIS AND TREATMENT OF LIVER CELL CANCER.

Tsung-Tang S, Zhao-You T, Yuan-Yun C

Cancer Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

Possible etiological factors, mechanism of carcinogenesis, early diagnosis, and surgical treatment of liver cell cancer are reviewed. Topics include epidemiology (geographic distributions, hepatotoxins, hepatitis B virus, host factors, prevention trials), early diagnosis (alpha fetoprotein serology, hepatoangiography, ultrasonography, computerized tomography, radionuclide imaging, tumor markers other than alpha fetoprotein), and treatment (early treatment of mass survey patients and ultimate outcome, surgical resection, surgical approach to nonresectable cases, conservative treatment of liver cell cancer). (147 Refs)

78. TRANSLATION OF PHARMACOKINETIC/ BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

Basic pharmacokinetic principles and biochemical mechanisms which must be considered in order to adequately evaluate the risk of exposure to man from potentially carcinogenic chemicals are reviewed. Dose-independent and dose-dependent pharmacokinetics are discussed. A theoretical model describing the pharmacokinetics of chemical interactions with macromolecules is presented, with emphasis on the importance of knowledge of the dose-related fate of a chemical and its macromolecular target site. Two basic mechanisms responsible for the observation of increased tumor frequencies in the typical animal bioassay are the genetic or genotoxic mechanism and the mechanism through which tumors are produced by a cytotoxic or nongenetic effect. Studies of vinyl chloride (VC) and chloroform illustrate the use of pharmacokinetic and biochemical data of the mechanisms of tumorigenesis to understand the differential carcinogenic response between species with emphasis on risk assessment. With VC, the incidence of hepatic angiosarcomas in humans can be predicted with reasonable accuracy using a probit percentage incidence model. The primary mechanism by which chloroform produces tumors in animal bioassays appears to be recurrent cytotoxicity accompanied by chronic tissue regeneration. The original risk estimation of chloroform was found to be unjustified and overestimated when the species dependent metabolic activation of the compound and the biochemical nature of chloroform-induced tumorigenicity were considered. (38 Refs)

79. METHYLDOPA AND BILIARY CARCINOMA: AN INTERNATIONAL STUDY OF SECULAR TRENDS (MEETING ABSTRACT)

Strom BL, Hibberd PL, Stolley PD

Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

Eighty-third Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, March 17-20, 1982, Lake Buena Vista, Florida. American Society for Clinical Pharmacology and Therapeutics 87 pp., 1982.

An association between methyldopa and biliary carcinoma was reported recently, but errors in study design make the result difficult to interpret. We have reexamined this possible association. Incidence or mortality rates of biliary carcinoma were obtained from 18 cancer registries throughout the world, both before and after methyldopa was marketed. Methyldopa sales were obtained from both its manufacturer and a commercial prescription audit. For each registry, sex-specific age-adjusted rates of biliary carcinoma was correlated with methyldopa sales, over time. In each year, methyldopa sales were correlated with sex-specific age-adjusted rates of biliary carcinoma obtained from each registry to study international trends. Both a 3-and 10-yr lag period was used in all analyses. No trends were observed in rates of biliary carcinoma, except in national mortality data obtained from Japan. No significant association between cancer rates and sales were discovered over time in 17 of 18 registries, again except in Japan, We did not observe any international trends. Further examination of the Japanese data showed that the association between sales and cancer rates persisted for all lag periods between 3 and 12 yr and for all subcategories of biliary carcinoma. Thus, we conclude that the association observed in the Japanese data is probably due to coincidence and that there is no association between biliary carcinoma and methyldopa sales. (no Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.
Davidson IW, Sumner DD, Parker JC
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Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.
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7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.
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8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.
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INSERM Symp; 19:3-11 1981

9. PATHOLOGY.
Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

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10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
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11. RISK OF RADIOLOGICAL EXAMINATIONS.
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12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)
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IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

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14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.
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15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.
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16. CAFFEINE: AN UPDATE.
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17. ANALYSIS OF MUTAGENIC EFFECTS OF FOREIGN SUBSTANCES IN THE FOOD PRODUCTS.
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

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148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.
Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.
Svoboda DJ, Reddy J
Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.
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34. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS.
Ludlum DB, Tong WP
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35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.
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36. METABOLISM AND TOXICITY OF AFLATOXINS.
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Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616
Adv Exp Med Biol; 136(partB):847-863 1982

37. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.
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38. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

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Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, Wurzburg D-8700, W. Germany

Adv Exp Med Biol; 136(partA):659-666 1982

39. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

Adv Exp Med Biol; 136(partA):693-701 1982

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

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MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

Hepatogastroenterology; 28(4):221-228 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

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45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

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Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. MORTALITY AMONG RUBBER WORKERS: V. PROCESSING WORKERS.

Delzell E, Monson RR
Duke Univ. Comprehensive Cancer Center, Durham, NC
JOM; 24(7):539-545 1982

Cause-specific mortality was evaluated among 2,666 men employed in the processing division of a rubber manufacturing plant. The division was divided into two sections: front processing (compounding, mixing and milling operations) and back processing (extrusion, calendering, cement mixing and rubberized fabrics operations). Mortality rates for all processing workers combined and for men in each section were compared with rates for US white males or for workers employed in other divisions of the same plant. Compared with either referent group, men in the processing division had increased mortality from leukemia, emphysema, and cancers of the stomach, large intestine, and biliary passages and liver. An excess number of deaths from stomach and large intestine cancer was

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found predominantly among men in the front processing section (33 observed vs 17.7 expected deaths, based on rates in nonprocessing workers). Increased mortality from leukemia (14 observed vs 7.3 expected) and from emphysema (22 observed vs 11.0 expected) was present among men employed in the back processing section. Examination of mortality from these causes according to age and the yr starting work, duration of employment, and yr since starting work in the relevant sections of the processing division suggested that observed excesses of stomach cancer, large intestine cancer, leukemia, and emphysema among processing workers are related to occupational exposures. These results are consistent with the findings of studies of other groups of rubber workers. (Author abstract) (20 Refs)

2. EXTRAHEPATIC MALIGNANCY AND ATHEROSCLEROSIS IN PRIMARY BILIARY CIRRHOSIS (MEETING ABSTRACT).

Wolke A, Brooks K, Sacks H, Schaffner F
Department of Medicine, Mount Sinai School of Medicine, New York, NY, 10029
Gastroenterology; 82(5,part2):1212 1982

From 1958-1981 we followed 208 patients with primary biliary cirrhosis. Twelve cases of cancer occurred, eleven were found to have an extrahepatic malignancy and one was found to have hepatocellular carcinoma. This is 2.9 times the incidence expected from the rate of cancer prevailing in a comparable population. This figure results from a 4.4 times greater incidence of breast cancer while the occurrence of non-breast and hepatocellular carcinoma was not significantly increased. Atherosclerosis as manifested by classical angina, myocardial infarction or symptomatic peripheral vascular disease was remarkably prominent in the male subgroup. Seven out of 21 men and 7/187 females met our criteria for the presence of atherosclerosis with our male population having a 7.1 times greater incidence of atherosclerosis than an age matched control. The 2.9 times greater incidence of atherosclerosis in our female population was not statistically significant. Although cholesterol levels were evaluated in our patients there were no trends toward high cholesterol nor lower high density lipoprotein fractions in those with atherosclerosis. Likewise other coronary risk factors were poorly predictive. Primary immunologic disorders may be associated with an increase risk of developing coronary artery disease and neoplasia and this factor in our patients with primary biliary cirrhosis, an assumed autoimmune disease, may explain these associations. The morbidity and mortality of these conditions emphasizes the need for close surveillance for breast cancer in females and of coronary risk factors in males with primary biliary cirrhosis. (3 Refs)

TUMOR INDUCTION IN ANIMALS

3. INFLUENCE OF AGE ON HEPATOCARCINOGENESIS IN RATS INGESTING DIETHYLNITROSAMINE.

Mochizuki Y, Furukawa K
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Tumor Res (Sapporo); 16:19-28 1981

The effect of increasing age on the incidence of hepatocellular carcinoma induced in male Fischer rats by diethylnitrosamine (DEN) was investigated. The av amounts of daily intake of DEN per rat in Group I (3 mo old), II (6 mo old), III (9 mo old) and IV (12 mo old) were 0.77, 1.16, 0.83, and 1.03 mg, and total amounts were 53.6, 81.0, 57.8, and 72.2 mg, respectively. All rats in Group I had liver tumors larger than 5 mm in diameter. The av number of tumors larger than 5 mm in diameter in Group I was 8.30. In Group II, 75% of rats had tumors larger than 5 mm, the av number of which was 2.25 per rat. In Group III, 60% of rats had tumors larger than 5 mm. Av number of tumors per rat was 1.80. In Group IV, 63% of rats had tumors larger than 5 mm, the av number of which was 2.00 per rat. Differences were statistically different between Group I and Group II-IV. The mechanisms by which older animals are more refractory to DEN induction are discussed. (27 Refs)

4. INHALATION EXPOSURE OF RATS TO VAPORS OF 1-NITROPROPANE AT 100 PPM.

Griffin TB, Stein AA, Coulston F

Coulston International Corporation, White Sands Res. Center, 2512 Christina Place, Alamagordo, NM, 88310

Ecotoxicol Environ Saf; 6(3):268-282 1982

Rats were exposed by inhalation to 100 ppm 1-nitropropane (1-NP) for 7 hr per day, 5 days per wk, and sacrificed animals were examined at 1, 3, 12, and 18 mo, and at terminal sacrifice (21.5 mo). Gross and microscopic appearance of tissues and organs; histopathologic appearance; incidence of hepatocarcinomas; body wt; wt of liver, kidney, and brain; serum chemistry; hematology; and apparent behavior were all unaffected by 1-NP treatment. (3 Refs)

5. INDUCTION OF HEPATOCELLULAR NUCLEOSIDE-5'-TRIPHOSPHATASE (ATPASE) DEFICIENT FOCI BY VINYL CHLORIDE (VC) (MEETING ABSTRACT).

Laib RJ, Bolt HM

International Agency for Research on Cancer, 69372 Lyon Cedex 2, France

Proc Am Assoc Cancer Res; 23:231 1982

In many species including man, VC induces angiosarcomas originating from endothelial cells of the liver, while in newborn rats, hepatocytes are more susceptible. This effect can be quantified by evaluating preneoplastic hepatocellular foci with ATPase deficiency. Rats were exposed to 2000ppm VC (8hrs/day), either transplacentally (schedule A) or immediately after birth for different time intervals (B-E), and from the age of 21 days onwards (F). Four-month old animals were sacrificed and the livers evaluated histochemically for ATPase deficient foci. Transplacental exposure (A) and schedule B revealed no increase in ATPase deficient foci, possibly due to the low rate of VC metabolism at this developmental stage. The % foci increased from schedule C to D but was not further enhanced after prolonged exposure (E). Only a few ATPase deficient foci were observed when exposure started 21 days after birth (F). As shown previously, a 70 day exposure of adult female rats to VC also did not result in ATPase deficient foci. These results indicate that the initiation of preneoplastic lesions of VC in rat hepatocytes is restricted to the early lifetime and that VC does not exert a substantial growth-promoting effect on induced ATPase deficient foci. (1 Ref)

MODIFICATION OF HEPATOCARCINOGENESIS

6. SELENIUM AND THE ACUTE EFFECTS OF THE CARCINOGENS, 2-ACETYLAMINOFLUORENE AND METHYLAZOXYMETHANOL ACETATE.

Banner WP, Tan QH, Zedeck MS

(c/o Zedeck) Lab. Pharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

Cancer Res; 42(8):2985-2989 1982

Selenium inhibits the development of 2-acetylaminofluorene-induced hepatic tumors and methylazoxymethanol-induced colon tumors. It has been suggested that selenium exerts these protective effects by inhibiting metabolic activation of the carcinogen. We have studied the effects of selenium upon the acute inhibition of RNA and DNA synthesis induced by 2-acetylaminofluorene or methylazoxymethanol in intact liver, regenerating liver, and colon of weanling male Sprague-Dawley rats. Some animals received selenium in the drinking water (4 ppm) for 1 wk, while others received a single injection of selenium (1 mg/kg ip) prior to being treated with the carcinogens. No protection against the effects of the carcinogens on RNA or DNA synthesis was noted with either treatment of selenium. Disulfiram did protect against the 2-acetylaminofluorene-induced inhibition of hepatic RNA synthesis, and pyrazole prevented the inhibition of RNA synthesis induced by methylazoxymethanol in both liver and colon. Serum selenium levels are reported. The data indicate that selenium does not influence the acute alterations induced by the carcinogens 2-acetylaminofluorene or methylazoxymethanol and suggest that the tumor-preventive effects of selenium are probably due to a mechanism other than interference with carcinogen activation and interaction with cellular macromolecules. (Author abstract) (34 Refs)

7. EFFECT OF SELENOSEMICARBAZIDE ON EXPERIMENTAL LIVER CARCINOGENESIS.

Tepliakova GV, Mekhtiev MA, Tagi-Zade SB, Karaeva EM, Alieva NB, Guseinova RA

Res. Inst. Roentgenology, Radiology, and Oncology, Baku, USSR

Eksp Onkol; 4(3):71-73 1982

Effect of selenosemicarbazide (SSC) on liver carcinogenesis was studied in random-bred rats. The rats received the carcinogen thioacetamide (TAA) alone or in combination with the SSC (2 mg/kg, sc). TAA-induced changes in the liver included dystrophy and necrosis during wk 4-8 of the experiment, replacement of liver tissue by connective tissue (wk 10-12), development of cirrhosis and cholangioadenomas (wk 16-20), and formation of malignant cholangiocarcinomas (wk 28). Benign and malignant liver tumors were observed in 95% of the rats exposed to the TAA. SSC administration inhibited, but did not prevent, the development of liver changes. It stimulated hematopoiesis and phagocytosis, enhanced the antiradical activity of liver lipids, and increased the activity of liver lactate dehydrogenase. It did not affect survival of the rats during the first 2-3 mo of the experiment. After 7.5-mo, survival rate in the animals treated with both TAA and SSC was 1.4x greater than that in the animals treated with TAA alone. (15 Refs) (In RUS)

8. EFFECT OF THE DRUGS METHAPYRILENE AND NAFENOPIN ON CARCINOGEN-INDUCED ALTERED FOCI IN RAT LIVER (MEETING ABSTRACT).

Furuya K, Furukawa K, Mori H, Williams GM, Levine W

Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Proc Am Assoc Cancer Res; 23:400 1982

Methapyrilene, an antihistimine and nafenopin, a hypolipidemic agent, have produced liver tumors in rodents, but have shown no evidence of genotoxicity. To determine if these drugs could act as liver tumor promoters, they were fed at 0.05 and 0.1% to F344 rats for up to 24 weeks after the induction of hepatic altered foci by feeding of 0.02% N-2-fluorenylacetamide (FAA) for 8 weeks. The effect of the drugs on FAA-induced altered foci identified by resistance to iron accumulation (IR) and gamma-glutamyl transpeptidase (GGT) activity was compared to that of the liver tumor promoter phenobarbital which enhances the progression of foci to neoplasms. Like phenobarbital, methapyrilene at 0.1% increased the numbers of both IR and GGT-positive foci (6x and 3x respectively) and neoplastic nodules (10x), but not carcinomas, relative to rats returned to the control diet. Nafenopin at 0.1% decreased the numbers of GGT-positive foci by more than 0.3 although IR foci were almost the same as in controls. The number of neoplastic nodules was also reduced by more than 0.5 in the nafenopin group. Thus, methapyrilene like phenobarbital displayed a substantial enhancing effect on hepatocarcinogenesis following FAA while nafenopin was inhibitory. (no Refs)

9. PROMOTION BY PHENOBOARBITAL (PB) OF CARCINOGENESIS INITIATED BY N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]FORMAMIDE (FANFT) (MEETING ABSTRACT).

Wang CY, Garner CD, Hirose M

Michigan Cancer Foundation, Detroit, MI, 48201

Proc Am Assoc Cancer Res; 23:403 1982

The present study investigated whether FANFT also initiates liver tumors and PB promotes bladder tumors. Weanling male Fischer rats were divided into 4 groups: I, fed Wayne Lab Blox for 7 wks followed by AIN (American Institute of Nutrition)-76 diet; II, fed the same as I except that the AIN Diet contained 0.05% PB; III, fed Wayne diet containing 0.2% FANFT for 6 wks, followed by 1 wk with Wayne diet, and then by AIN diet; and IV, fed the same as III except that the AIN diet contained 0.05% PB. The experiment was terminated at the end of 93 wks. Rats in III and IV ingested approx 1.2 g FANFT each. The effective number of rats were 27 (I), 24 (II), 40 (III), and 42 (IV), and survival times (wks) were 90 (I); 86 (II); 89 (III); and 87 (IV). The number of rats bearing bladder papillomas and carcinomas, respectively, were 4 and 17 (III), and 4 and 28 (IV). The incidence of bladder carcinomas in IV was significantly greater than in III. Neither I nor II had bladder tumors. The number of rats bearing hepatic cellular-altered foci and neoplastic nodules, respectively, were: 4 and 0 (I); 8 and 1 (II); 7 and 1 (III); and 23 and 6 (IV). The number of hepatic gamma-glutamyltranspeptidase (GGT) foci/cm2 were: 0.12 (I); 1.40 (II); 0.28 (III); and 5.52 (IV) in the rats surviving to the 93rd wk. The number of GGT foci in IV was significantly greater than in the other groups. (no Refs)

10. STRUCTURE-SPECIFIC DINITROTOLUENE (DNT) PROMOTION OF INITIATED HEPATOCYTES (MEETING ABSTRACT).

Leonard TB, Lyght O, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:399 1982

Technical grade DNT (tDNT), containing principally the 2,4-(76%) and 2,6-(20%) isomers, is a potent hepatocarcinogen when fed to male F-344 rats for 1 yr (100% incidence). These studies were designed to assess the promoting activity of 2,4- and 2,6-DNT. Male F-344 rats were initiated with a single dose of diethylnitrosamine (DEN) (150 mg/kg; ip) or saline (controls) then fed either 2,4-DNT (27 mg/kg/day) or 2,6-DNT (10 mg/kg/day) for 12 wk. Promoting activity was quantitated by determining the number of histochemically identifiable gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 2,4-DNT to DEN initiated animals markedly increased GGT+ foci (546/cm(3)) relative to controls (0/cm(3)). Whereas 2,4-DNT alone had little effect on foci incidence, feeding 2,6-DNT alone significantly elevated the background incidence of GGT+ foci (571/cm(3)). When combined with DEN initiation, 2,6-DNT enhanced the number (867/cm(3)) but not the average diameter of GGT+ foci present. These results, together with previously reported initiation data, support the conclusion that 2,6-DNT is a potent hepatocarcinogen with both initiating and promoting activity. In addition, these data indicate that 2,4-DNT also has hepatic promoting activity which likely contributes to DNT carcinogenesis. In conclusion, the carcinogenic activity of tDNT is largely accounted for by the initiating and promoting activity of 2,6-DNT. (no Refs)

11. FAILURE OF PHORBOL ESTER TPA TO PROMOTE GROWTH OF IN VIVO-INITIATED RAT HEPATOCYTES TRANSFERRED INTO A CULTURE SYSTEM.

Kayano T, Nomura K, Hino O, Kitagawa T
Dept. Pathology, Cancer Inst. Tokyo, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Gan; 73(3):354-357 1982

The effect of 12-O-tetradecanoylphorbol-13-acetate (TPA), a potent promoter in epidermal carcinogenesis, on the growth of rat hepatocytes initiated in vivo and transferred into a culture system was investigated. The hepatocytes were isolated by enzymatic perfusion from the rat liver after 12 wk of acetylaminofluorene feeding or 2 to approx 6 wk of diethylnitrosamine treatment. TPA did not show any promotive effect in terms of the number and size of proliferative epithelial cell foci derived from initiated hepatocytes, in contrast to the remarkable effect of phenobarbital, which is a potent promoter in hepatocarcinogenesis. The results suggest the existence of organ or target cell specificity of promoters in the two-stage concept of carcinogenesis. (Author abstract) (16 Refs)

12. CHEMICAL HEPATOCARCINOGENESIS IN INFANT MICE FOLLOWING A SINGLE ADMINISTRATION OF TESTOSTERONE AT THE NEONATAL STAGE.

Toh YC
Dept. Physiology, Univ. New England, Armidale, New South Wales, 2351, Australia
IRCS Med Sci [Cancer]; 9(11):1044 1981

BALB/c mice were injected sc with 100 ug testosterone propionate at the age of 2 days, then fed a diet containing N-2-fluorenylacetamide (FAA, beginning at 1 wk of age qod to a total dose 10.5 mg). At the age of 1 yr, hepatocellular tumors were found in 21% of male mice given FAA, 11% of female mice given testosterone then FAA, and in none of the female mice given FAA without testosterone. Thus, a single injection of testosterone propionate to neonatal female mice enhanced carcinogenicity of FAA, although male mice still had a higher incidence of hepatic lesions. (5 Refs)

13. ESTRADIOL SUPPRESSES 2-AAF HEPATOCARCINOGENESIS IN MALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

Griffin MJ
Oklahoma Medical Research Foundation, Oklahoma City, OK. 73104
Proc Am Assoc Cancer Res; 23:919 1982

Twenty-two male Sprague Dawley rats (100 +/-8 gr) were fed a diet containing 0.05% 2-AAF for 16 weeks in an interrupted fashion (3 weeks with 2-AAF, one without). Each day eleven rats received (ip) 0.2 ml of stripped corn oil (CO) while the other eleven received 0.2 ml of oil containing 1 mg of suspended estradiol (ES). The animals, fed ad lib, gained weight over the next 120 days at an average of 0.5 gr/day/rat (ES) versus 1.8 gr/day/rat (CO). After 120 days, the ES treated rats had atrophied testes containing few cells while the CO rats testes appeared normal. At 90 and 120 days, hyperplastic nodules were very prominent in the CO rat livers and this was confirmed by histochemical staining of liver sections for gamma GT. The ES rats had neither gross appearing hyperplastic liver nodules, nor did gamma GT histochemistry indicate nodules. However, a few areas in the ES liver sections stained for gamma GT in a fashion reminiscent of remodeling areas. Microsomal styrene oxide hydrolase activity was induced to 147 +/-16 nmol/min/mg protein in CO livers. ES suppressed this induction to 31 +/-8 nmol/min/mg protein). Preliminary data on tumor incidence at 210 days showed two (of two) CO rats with pathologically certified carcinomas and two ES rats without tumors. The remainder of the rats will be scored for death due to hepatoma. ES may have a direct effect on male rat liver membrane enzyme regulation, since ES has been reported detected in male rat liver endoplasmic reticulum. (no Refs)

14. SYNERGISTIC ACTION OF 13-CIS-RETINOIC ACID (CRA) AND 2,6-DIMETHYLNITROSOMORPHOLINE (DMNM) ON THE INDUCTION OF HEPATIC HEMANGIOMAS AND HEMANGIOSARCOMAS IN SYRIAN GOLDEN HAMSTERS (MEETING ABSTRACT).

Stinson SF, Reznik G, Levitt MH
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:225 1982

During a study designed to test the effect of CRA on the induction of a broad spectrum of neoplasms induced by DMNM, an increase in the incidence of hepatic hemangiomas and hemangiosarcomas was observed in animals given both CRA and DMNM. Groups of 40 male Syrian golden hamsters were given weekly doses of 0, 40, 80 or 160 mg/kg DMNM for 10 weeks. Twenty animals in each group were dosed ig, and the remainder sc. A duplicate series of hamsters was treated in a similar manner except that they were maintained on a diet supplemented with 160 mg/kg CRA. Twelve animals from each group were necropsied at 15, 25, and 40 weeks (six each from ig and sc dosing regimens). Others were killed when moribund. Results by ig and sc routes were comparable. There was no significant difference in time related mortality between hamsters receiving or not receiving CRA, although weight gain was less in those given CRA. There was an increase in the number of hamsters with hepatic hemangiomas or hemangiosarcomas with increasing levels of DMNM except in the 160 mg/kg group which had substantial early mortality due to DMNM toxicity. These neoplasms were observed in 43/120 hamsters given CRA and DMNM but in only 5/120 given DMNM alone. No neoplasms were found in 40 hamsters given CRA alone. These results indicate synergistic action of DMNM and CRA in the induction of hepatic hemangiomas and hemangiosarcomas. (no Refs)

15. EFFECT OF DIETARY FAT AND ANTIOXIDANT ON INCIDENCE OF SPONTANEOUS AND 1,2-DIMETHYLHYDRAZINE-INDUCED TUMORS IN MICE (MEETING ABSTRACT).

Brown RR, Erturk E, Arend RA, Potera C, Remus N, Ruzicka E, Dallmann L
University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:277 1982

In attempts to further define the role of type and quantity of dietary fat and antioxidants on cancer incidence, we studied tumor incidence (spontaneous and dimethylhydrazine (DMH) induced) in mice fed semipurified diets having one of 5 different vegetable fat mixes containing respectively 59% saturated (SAT), 60% monoene (MUF), 59% diene (DUF), 35% transmonoene (TRN), or 4% triene (TUF). Butylatedhydroxyanisole (BHA) was added to some SAT and TUF diets. Weanling CD-1 mice of both sexes (40/group) and female C3H (60/group) were fed these diets having 5% or 17% fat substituted isocalorically for sucrose. Treated mice received 10 weekly subcutaneous injections of 0.25 mg DMH freshly neutralized. Controls received buffer only. DMH caused liver tumors and a few kidney and lung tumors and splenic leukemia, but no colon tumors. More DMH-induced liver and lung tumors were seen in males fed 5% TRN than in other groups but this was not confirmed in males fed 17% TRN. Total tumors in males fed 17% and 5% fats were not different suggesting that when fed isocalorically, the quantity of fat did not influence tumor incidence in CD-1 males. BHA reduced the DMH-liver tumor rate in 17% SAT but not in 17% TUF. DMH-liver tumors were fewer in 17% SAT than in 17% TUF males and this difference was even greater between SAT+BHA+DMH and TUF+BHA+DMH groups. (no Refs)

16. INHIBITION OF AFLATOXIN-INITIATED PRENEOPLASTIC LIVER LESIONS BY LOW DIETARY PROTEIN.

Appleton BS, Campbell TC
Div. Nutritional Sciences, Cornell Univ., Ithaca, NY
Nutr Cancer; 3(4):200-206 1982

The development of aflatoxin B1-induced hepatic preneoplastic lesions was significantly modified by varying the level of dietary casein fed to animals during the post-dosing period. Using gamma-glutamyl transferase staining to identify areas of cellular alteration, we observed that animals fed a 5% casein diet showed a 75% reduction in lesion development as compared to animals fed a 20% casein diet. Increasing the level of dietary casein from 20% to 40% produced no further increase in response. The results of study, showing an inhibition in the preneoplastic development by a reduction of dietary casein after aflatoxin dosing, suggest that low dietary casein inhibits the promotional phase of the ultimate neoplastic response. (Author abstract) (24 Refs)

17. MODIFICATION OF N-DIETHYLNITROSAMINE-INDUCED CARCINOGENESIS BY CLONIDINE, CAFFEINE, AND ETHANOL.

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N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Eksp Onkol; 4(3):25-29 1982

Roles of adrenergic and cholinergic receptors in the mechanism of chemical carcinogenesis were studied in random-bred male rats. The rats received drinking water containing N-diethylnitrosamine (DENA: 70 mg/liter) for 4 mo. Rats in Group 1 received DENA alone those in Group 2 received DENA in combination with clonidine (0.05 mg/kg, ip), those in Group 3 received DENA in combination with ethanol (2 ml/rat, po), and those in Group 4 received DENA in combination with caffeine (3.5 mg/kg, sc). The animals were sacrificed 6 mo after initiation of the experiment, and growths of esophageal and liver tumors that were induced were determined. Histological examination of neoplastic changes in the esophagus and liver showed that caffeine stimulated the DENA-induced carcinogenesis, while clonidine and ethanol inhibited the carcinogenesis. Therapeutic administration of clonidine produced marked inhibition of the DENA-induced liver tumors. Changes in acetylcholinesterase activity in the brain during the DENA carcinogenesis indicated that the modifying effects of clonidine, caffeine, and ethanol were associated with stimulation and inhibition of the autonomic nervous system. (25 Refs) (In RUS)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

18. LABELED 1,N(6)-ETHENOADENOSINE AND 3,N(4)-ETHENOCYTIDINE IN HEPATIC RNA OF MICE GIVEN [ETHYL-1,2-3H OR ETHYL-1-14C] ETHYL CARBAMATE (URETHAN).

Ribovich ML, Miller JA, Miller EC, Timmins LG
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Carcinogenesis; 3(5):539-546 1982

Injection of a single dose of [ethyl-1,2-3H] or [ethyl-1-14C]ethyl carbamate into 12-day old male [C57BL/6 x C3H/He]F1 mice or of [ethyl-1,2-3H]ethyl carbamate into adult male A/Jax mice resulted in the formation of labeled 1,N6-ethenoadenosine and 3,N4-ethenocytidine adducts in the hepatic RNA. These adducts were characterized by comigration on hplc of 3H or 14C in enzymatic hydrolysates of the RNA with synthetic standards. Both the ethenoadenosine and ethenocytidine were further characterized by their conversion to acetylated products that comigrated with acetylated synthetic standards. The ethenoadenosine was also converted by anhydrous trifluoroacetic acid to a product that comigrated with synthetic 1,N6-ethenoadenine. The levels of adducts in the hepatic RNA 12 hr after a single injection of 0.5-0.6 mg of ethyl carbamate/g body wt were 6-10 and 2-3 pmol/mg RNA of ethenoadenosine or ethenocytidine, respectively. No labeled ethenoadenosine or ethenocytidine could be detected in the hepatic RNA of mice given [1-14C]ethanol, an enzymatic hydrolysis product of ethyl carbamate. These data indicate that ethyl carbamate may be metabolically activated by dehydrogenation to vinyl carbamate and subsequent epoxidation of the latter compound as previously proposed. Vinyl carbamate epoxide may form etheno derivatives in a manner analogous to that demonstrated for chloroethylene oxide, an electrophilic metabolite of vinyl chloride. Vinyl carbamate has been shown to have the same spectrum of tumor induction as ethyl carbamate but to be much more active than the latter carcinogen. (Author abstract) (37 Refs)

19. EFFECTS OF DIETARY AND IN VITRO 2(3)-T-BUTYL-4-HYDROXYANISOLE AND OTHER PHENOLS ON HEPATIC ENZYME ACTIVITIES IN MICE.

Rahimtula AD, Jernstrom B, Dock L, Moldeus P
Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland A1B 3X9, Canada
Br J Cancer; 45(6):935-944 1982

Six phenols [2(3)-t-butyl-4-hydroxyanisole (BHA), 2-t-butylphenol, 4-methoxyphenol, 4-methylmercaptophenol, t-butylhydroquinone and 2,6-di-t-butylphenol] previously shown to be inhibitors of benzo(a)pyrene-induced neoplasia, were examined for their ability to induce in vivo changes in hepatic mono-oxygenase and detoxication enzyme activities, and to act as mono-oxygenase inhibitors when added in vitro. (1) Generally it was found that cytochrome P450 levels were depressed, only 2,6-di-t-butylphenol caused a two-fold induction (2) Mono-oxygenase activities were significantly altered; BHA and 2,6-di-t-butylphenol caused microsomes to show substantial increases in aniline hydroxylase and peroxidase activities. These microsomes, along with 4-methoxyphenol microsomes, also showed a substantial reduction in DNA binding of benzo(a)pyrene (BaP) metabolites relative to metabolism. (3) Detoxication enzymes glutathione S-transferases and epoxide hydratase were readily induced, the order of effectiveness being: BHA approx = 2,6-di-t-butylphenol greater than 4-methoxyphenol greater than 2-t-butylphenol approx = 5-butylhydroquinone (4-methylmercaptophenol failed to induce). (4) In vitro ability to inhibit BaP metabolism and DNA-binding ability was: 2,6-di-t-butylphenol greater than or equal to BHA approx = 2-5-butylphenol greater than 5-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. (5) Ability in vitro to discharge the activated oxygen complex of cytochrome P450 was: 2,6-di-t-butylphenol approx = 2-t-butylphenol greater than BHA greater than t-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. The results are consistent with the theory that inhibition of neoplasia is related to inducibility of detoxication enzymes, though alterations in cytochrome P450 could play a significant role in some cases. (Author abstract) (39 Refs)

20. ENHANCED HEPATOTOXICITY OF AFLATOXIN B1 BY PRETREATMENT OF RATS WITH ETHANOL.

Toskulkao C, Taycharpipranai S, Glinsukon T
Dept. Physiology, Faculty Science, Mahidol Univ., Rama VI Road, Bangkok 4, Thailand
Res Commun Chem Pathol Pharmacol; 36(3):477-491 1982

Hepatotoxicity of aflatoxin B1 (2.0 and 4.0 mg/kg ip) as determined by plasma enzyme activities (GPT and GOT), liver triglycerides and histopathologic changes was enhanced in rats pretreated with four oral doses of ethanol (4.0 g/kg each) at 48, 45, 24 and 21 hr prior to aflatoxin B1 administration. Pretreatment with ethanol (4.0 g/kg) slightly increased liver weight without changing hepatic microsomal protein contents. Also it caused an increase in microsomal aniline hydroxylase but a decrease in p-nitroanisole-o-demethylase, 48 hr after the first ethanol dose. In the rats pretreated with ethanol, aflatoxin B1 was metabolized at a higher extent to aflatoxins M1 and Q1. These results suggest that an increased hepatotoxicity of aflatoxin B1 after pretreatment with ethanol may presumably be due to an increase in microsomal formation of active aflatoxin B1 metabolite. (Author abstract) (36 Refs)

21. LIVER NEOPLASIA AND INDUCTION OF HEPATIC MIXED FUNCTION OXIDASE ENZYMES IN THE RAINBOW TROUT FOLLOWING DIETARY EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

Hendricks JD, Meyers TR, Shelton DW, Sinnhuber RO
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Proc Am Assoc Cancer Res; 23:226 1982

The influence of benzo(a)pyrene (BP) on the induction of certain enzymes within the hepatic mixed function oxidase (MFO) system and its potential carcinogenicity were examined in rainbow trout during a continuous dietary exposure. Nine week feeding trials were performed using 500 and 1000 ppm of BP to determine the maximum tolerated dose (MTD) without producing fish mortalities or growth inhibition. Levels of MFO enzymes including ethoxyresorufin-O-deethylase (EROD), ethoxycoumarin-O-deethylase (ECOD), arylhydrocarbon hydroxylase (AHH) and cytochrome P-450 were measured during this time. A feeding trial using a MTD of 1000 ppm was initiated in duplicate groups of 100 fingerling rainbow trout. Trout were sampled at 6, 12 and 18 months for necropsy and subsequent gross and histological examination of internal organs. Mean MFO enzyme levels of EROD, ECOD, and AHH were significantly elevated showing dose and time response relationships when compared to those of fish fed a BP-free diet. P-450 levels in BP-fed fish increased only slightly. At 12 months 15% of the BP-fed fish had histologically confirmed neoplastic lesions of the liver. After 18 months 20% gross lesions were observed, histological confirmation is in progress. No evidence of neoplasia was observed in control fish. These results indicate that in rainbow trout BP is a potent inducer of certain hepatic MFO enzymes and is a hepatocarcinogen when fed continuously in the diet. (no Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

22. CLONING AND STRUCTURAL ANALYSIS OF INTEGRATED WOODCHUCK HEPATITIS VIRUS SEQUENCES FROM HEPATOCELLULAR CARCINOMAS OF WOODCHUCKS.

Ogston CW, Jonak GJ, Rogler CE, Astrin SM, Summers J
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Cell; 29(2):385-394 1982

Woodchuck hepatitis virus (WHV), like the related hepatitis B virus, induces in its natural host hepatocellular carcinomas that contain integrated viral sequences. As a first step in determining whether and how the integrated sequences contribute to formation of the tumors in which they are found, we have cloned two such integrations of WHV and have determined their structure by restriction mapping and heteroduplex electron microscopy. The identity of the cloned sequences was confirmed by comparison of restriction sites in the clones with those located by Southern blot analysis of tumor DNA. Viral sequences in both integrations are extensively rearranged, and in neither were all parts of the viral genome represented. In this respect, the behavior of WHV in vivo is similar to that of other DNA tumor viruses that have been studied in vitro. We discuss the implications of these results in relation to possible mechanisms for tumor induction by WHV. (Author abstract) (38 Refs)

23. HEPATITIS B VIRUS AND PRIMARY HEPATOCELLULAR CARCINOMA: FAMILY STUDIES IN KOREA.

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Int J Cancer; 30(1):47-51 1982

Chronic infection with hepatitis B virus (HBV) is closely associated with the etio-pathogenesis of primary hepatocellular carcinoma (PHC). It has been proposed that infection with HBV early in life, frequently transmitted by an HBV-carrier mother, leads to persistent infection with HBV, which in turn is associated with the development of chronic active hepatitis (CAH), post-necrotic cirrhosis and PHC. If this view is correct, then there should be clustering of chronic carriers of HBV in families of patients with chronic liver disease. We tested this hypothesis in Korea by collecting serum from 132 patients with these chronic liver diseases admitted to the Seoul National University Hospital and 664 of their first-degree relatives. Sera were assayed for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs) and antibody to hepatitis B core antigen (anti-HBc). Almost all cases showed evidence of present or past infection with HBV. Mothers of patients were more frequently HBsAg(+) than age-matched women in the control population or wives of patients. Five of 23 fathers were also HBsAg(+) compared with 1 of 25 age-matched controls. There was a deficit of anti-HBs in the fathers of cases compared with the controls. Siblings of patients were frequently HBsAg(+), with the highest prevalence in brothers. Family history shows that five fathers, two mothers and five brothers of cases have died of PHC. These data are compatible with the hypothesis tested and lend further support to the view that prevention of infection with HBV will lead to a marked decrease in the incidence of CAH, cirrhosis and PHC in areas where these diseases are endemic. Members of the families of patients with these diseases are at high risk of developing persistent infection with HBV and chronic liver disease. It would be appropriate to focus preventive strategies on infants and children in such families. (19 Refs)

24. INVESTIGATION ON THE RELATIONSHIP BETWEEN HBSAG AND PRIMARY HEPATIC CANCER (PHC) IN HOUSEHOLDS IN AREAS OF LOW RISK FOR PHC.

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Zhonghua Yufangyixue Zazhi; 15(5):296-298 1981

In order to study the relationship between hepatitis B infection and PHC, the positive rate for HBsAg and incidence of hepatitis in households of PHC, hepatitis and esophageal cancer were surveyed. Results showed that the number of patients with a past history of hepatitis was 7.1 x more in PHC than in esophageal cancer. Family members in the PHC group had markedly higher positive rates for HBsAg than those in esophageal cancer or healthy families. Significance of these findings is discussed. (7 Refs) (In CHI)

25. ANTIGENIC CHANGES IN NONHISTONE PROTEINS DURING AZO DYE HEPATOCARCINOGENESIS.

Schmidt WN, Gronert BJ, Page DL, Briggs RC, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 42(8):3164-3174 1982

We have investigated the appearance of specific nonhistone proteins during azo dye induced hepatocarcinogenesis in the rat. Groups of animals fed azo dye-containing diet were sacrificed at approx 3-wk intervals, portions of their livers were examined histologically, and the remaining material was fractionated into chromatin and cytoplasmic fractions. Livers of the azo dye-fed animals exhibited histological changes that have been classically attributed to the course and development of cancer; by 28 to 30 wk of treatment, nearly all animals had developed hepatomas. Heterogeneous rabbit antisera were prepared to dehistonized chromatin from several azo dye-induced hepatomas. These antisera were then used to assess various chromatins for the appearance of antigens specific for neoplasia during induced carcinogenesis using immunodetection of antigens separated electrophoretically and transferred to nitrocellulose. Changes in the immunoreactivity of liver chromosomal proteins during carcinogen treatment were evident after 3 wk, and the antigenic profiles of various chromatin samples gradually assumed the characteristics of the hepatoma. The transformation was accompanied by qualitative changes in chromosomal protein antigens, and although these antigenic species were not directly quantitated, noticeable enrichment of tumor-specific species occurred with treatment time. Immunotransfer assays of cytoplasmic fractions indicated most antigens to be specific for chromatin. Normal tissue chromatin exhibited minimal immunoreactivity, and slightly more antigenic homology was noted with regenerating liver and most transplantable tumor chromatins. Interestingly, the transplantable tumor Walker 256 carcinosarcoma was highly enriched in antigens recognized by antisera to azo dye hepatoma dehistonized chromatin. These studies establish a definite chronological correlation between the chemical induction of cancer and sequential changes in the immunological specificity of nonhistone protein antigens. (Author abstract) (56 Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

26. CHROMOSOMES OF HUMAN HEPATOMA CELL LINES.

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Int J Cancer; 30(1):27-33 1982

The karyotypes of three human hepatoma cell lines Hep G2, Hep 3B and PLC/PRF/5 were investigated by G-and C-banding techniques. In addition to ploidy changes, typical for most carcinoma cell lines, certain markers were found that remained stable throughout passage of these cultures. Chromosome 1 is involved in multiple translocations, resulting in at least three copies of the chromosome 1 heterochromatin region in each cell line. Inversion in the 9qh region is also seen. In addition, each of the cell lines consistently contains trisomy of 17q. The rearrangements of chromosome 1 are more striking in the Hep 3B and PLC/PRF/5 cell lines, which are derived from human hepatocellular carcinomas and contain integrated copies of the hepatitis B viral genome. These two cell lines are characterized by the presence of at least five copies of the 1 (p13 to q21) region that result from multiple deletions and/or translocations; by consistent trisomy and polymorphism of the 9qh region; and by trisomy of chromosome 10 (also involved in rearrangements). The Hep G2 and Hep 3B cell lines behave functionally as highly differentiated liver parenchymal cells and are karyologically distinguishable from PLC/PRF/5 both by the presence of trisomy of 6 (pter to q14) and by the finding that one of the homologues of chromosome 15 is 15q+. (Author abstract) (29 Refs)

27. ESTABLISHMENT OF A HUMAN TUMOR CELL LINE FROM A PATIENT WITH PRIMARY HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT).

He L, Wands JR, Quarcoi A, Isselbacher KJ
Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA, 02114
Gastroenterology; 82(5,part2):1080 1982

A tumor cell line designated CUSPF (China-United States Peoples Friendship) was established in long-term culture from a hepatitis B surface antigen (HBsAg) negative individual with a poorly differentiated primary hepatocellular carcinoma. The cultured cells have an epithelioid appearance by light and phase contrast microscopy. Scanning electron microscopy revealed extensive microvilli formation on the cell surface as well as communications between cells. Transmission electron microscopy demonstrated a polygonal morphology, with 'epithelioid like' junctions between cells, numerous mitochondria and smooth endoplasmic reticulum, but a poorly developed rough endoplasmic reticulum. Growth curves repeated three months apart were identical and demonstrate a doubling time of 48 hours. The CUSPF cells show loss of contact inhibition under confluent conditions. Human chromosomes were identified by isoenzyme analysis. The cells were shown to have aspartate aminotransferase (SGOT) activity but do not synthesize or secrete HBsAg or alpha fetoprotein. Monoclonal antibodies have been prepared to this cell line. The malignant potential of the CUSPF cell line was established by gross tumor formation when injected subcutaneously (1.4x10(7)) into nude mice. The morphology of the solid tumor closely resembles the original hepatocellular carcinoma. Finally, the properties of recultured cells derived from the solid tumor mass grown in nude mice appear to be identical to the original CUSPF cell line. Thus, we have established in culture a human hepatocellular carcinoma cell line. Such cells will be of use in characterization of the malignant properties of human hepatocytes. (no Refs)

28. A HUMAN HEPATOMA CELL LINE (PLC/PRF/5) PRODUCES LUNG METASTASES AND SECRETES HBSAG IN NUDE MICE.

Sattler FR, Paolucci S, Kreider JW, Ladda RL
500 University Drive, Hershey, PA, 17033
Eur J Cancer Clin Oncol; 18(4):381-389 1982

PLC/PRF/5 is a human liver cancer cell line which synthesizes hepatitis B virus surface antigen (HBsAg). These cells produced tumor in 6 of 8 (75%) congenitally athymic nude mice at 13 of 28 subcutaneous injection sites and in 13 of 14 (93%) mice inoculated intraperitoneally. Tumors were successfully transplanted to four of six additional nude mice. Tumor growth was rapid. Growth of cephalad tumors was significantly greater than for caudal tumors (0.39 mm/day vs 0.28 mm/day). Microscopic examination of tumors showed moderately well-differentiated hepatocellular carcinoma. Foci of identical cells were present in pulmonary veins in 7 of 14 tumor-bearing animals. Tumor cell karyotype was identical with that of PLC/PRF/5 cells. In addition, HBsAg was detectable in high titer in animals with extensive tumor. Biological features of PLC/PRF/5-induced tumors in nude mice appeared to closely resemble human hepatocellular carcinoma. Moreover, HBsAg may provide a marker of tumor growth. (Author abstract) (24 Refs)

29. MORPHOMETRIC COMPARISON OF THE ULTRASTRUCTURE OF NORMAL HEPATOCYTES AND CELLS FROM PRIMARY AND TRANSPLANTED, SAFROLE-INDUCED HEPATOCELLULAR NEOPLASMS IN MICE (MEETING ABSTRACT).

Zhou C, Lipsky MM, Tanner D, Trump BF
Department of Pathology, University of Maryland Medical School, Baltimore, MD, 21201
Proc Am Assoc Cancer Res; 23:220 1982

Cells from safrole-induced hepatocellular adenomas (HA), hepatocellular carcinomas (HPC) and transplanted HPC were characterized by morphometric analyses of cellular and subcellular components and compared to normal hepatocytes. Male Balb/c mice were fed safrole (4,000 ppm) for 1 year to induce hepatic neoplasms. Livers from 5 control mice, 5HA, 5HPC and 3 transplanted HPC were fixed and processed for routine electron microscopy. Electron micrographs from randomly sampled areas of appropriate tissues were analyzed with a Zeiss Videoplan using the appropriate computer programs for stereology and subsequent statistical analyses. Relative cell volume decreased from normal liver to HA to HPC. Nuclear volume increased slightly in a similar pattern. This resulted in an increase in the nuclear to cytoplasmic volume ratio from 7.1% for normal to 13.0% (HA), 12.6% (HPC) and 15.8% transplanted HPC. There was a slight decrease in the volume of rough endoplasmic reticulum in neoplastic cells coupled with a large increase in the volume of smooth endoplasmic reticulum (normal, 0.9%; HA, 3%; HPC, 4%), even in fifth generation transplanted HPC. An increase was also seen in the volume density of microbodies and autophagic vacuoles in neoplastic cells. The relative number and volume density of mitochondria, lysosomes and Golgi decreased slightly in neoplastic cells. (no Refs)

30. CLONAL GROWTH OF CARCINOGEN-INDUCED ENZYME-DEFICIENT PRENEOPLASTIC CELL POPULATIONS IN MOUSE LIVER.

Rabes HM, Bucher T, Hartmann A, Linke I, Dunnwald M
Pathologisches Institut, Universitat Munchen, Munich 2, W. Germany
Cancer Res; 42(8):3220-3227 1982

The cellular origin of preneoplastic subpopulations in liver during chemical carcinogenesis has not yet been clarified. An experimental approach to this problem became possible by using female phenotypic mosaics caused by the X-chromosome inactivation ('lyonization') occurring early in embryogenesis. Allozymes of the X-linked enzyme phosphoglycerate kinase (PGK-1) served as markers of the maternal (wild-type PGK-1B) and paternal (variant PGK-1A) X-chromosomes in crosses of near-congenic C3H mice. These PGK allozymes are of similar activity and stability but can be separated electrophoretically and quantified by a fluorimetric method. Pgk-1a/Pgk-1b heterozygous females were subjected to chronic 2-acetylaminofluorene feeding for up to 14 mo. Phenotypic expression of PGK-1B and PGK-1A was determined in ug samples as well as in mg samples of liver and other organs. Samples of adenosine triphosphatase-deficient preneoplastic populations punched out from cryostat serial sections of liver of 2-acetylaminofluorene-fed mice disclosed a PGK allozyme pattern strikingly different from the norm. Thirty-nine of 40 preneoplastic nodules contained a pure population of either PGK-1A or FGK-1B expressing cells. Mean contamination by the opposite PGK type was 1.1%. In all cases, the PGK expression in the preneoplastic nodules differed from the surrounding liver parenchyma. Only a single large hyperplastic nodule was composed of several subpopulations with respect to PGK expression. Determination in normal liver tissue of the patch size of coherent populations with a homogeneous expression of one PGK allozyme revealed an av of about eight hepatocytes per patch. Each microsample used for PGK determinations consisted of an av of 25 patches. It is evident from these results that AAF-induced, ATPase-deficient preneoplastic subpopulations in the mouse liver are in all probability clones derived from a single cell. (Author abstract) (43 Refs)

31. SEQUENTIAL CHANGES IN DIPLOID RAT LIVER EPITHELIAL CELLS TREATED WITH AFLATOXIN B1 IN CULTURE (MEETING ABSTRACT).

Iype PT, Currens MJ, Herring A, Kelley SP, McMahon JB, Ray-Chaudhuri R, Malan-Shibley L
National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:290 1982

Experiments were performed to analyze the chronology of the onset of transformation markers induced in rat liver cells by the hepatocarcinogen, aflatoxin B1 (AFL). A well-characterized, diploid liver epithelial cell line which exhibited no transformation markers was used at the tenth subculture. Three groups were studied. Group 1 consisted of untreated cells, Group 2, cells receiving a single treatment, and Group 3 cells given multiple exposures to the compound. The markers followed included altered karyology, loss of response to an hepatic proliferation-regulating protein (HPI), induced multinucleation by cytochalasin B, the presence of gamma-glutamyl transpeptidase (gamma-GT) and alpha-fetoprotein, the ability to bind concanavalin A coupled with agarose beads, the formation of colonies in soft agarose, and the growth of tumors in rats. Group 1 exhibited none of these characteristics for the 34 week duration of the study, except that aneuploid cells were seen in the population at 23 weeks. The earliest change seen in Groups 2 and 3 was a shift to a hyperdiploid karyology and the occurrence of marker chromosomes, which was followed by a loss of response to HPI, expression of gamma-GT, induction of multinucleation, growth in soft agar and tumorigenicity. Markers were observed at an earlier time in Group 3 compared with Group 2. The sequential appearance of these different markers might be indicative of progressive changes leading to malignancy. (no Refs)

32. EFFECT OF MICROSOMALLY ACTIVATED AFB1 ON GGT ACTIVITY IN 3 RAT LIVER CELL LINES.

Manson MM, Green JA
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Br J Cancer; 45(6):945-952 1982

Three cell lines derived from adult rat liver have been used to study changes in levels of gamma-glutamyltransferase (GGT), a possible marker for premalignant transformation in liver in vivo. None of the cell lines was able to metabolize aflatoxin B1 (AFB1) and treatment with AFB1 alone did not influence GGT activity. However, treatment with microsomally activated AFB1 increased the level of activity in a cell line (BL8L) derived from normal liver with very low levels of GGT, by as much as 10-fold, and 5-fold in a cell line (ARL) also isolated from normal rat liver, but which had subsequently undergone spontaneous transformation. Microsomes from rats pretreated with phenobarbitone were compared with those from 3-methylcholanthrene-treated animals. AFB1 activated by the former produced larger increases in GGT activity, but in no case did the enzyme levels approach that in a cell line (JBI) derived from a hepatoma in the liver of an AFB1-fed rat. Treatment of JBI cells with microsomally activated AFB1 produced no further increase in activity. Histochemical staining indicated an uneven distribution of enzyme in all cell populations, both before and after treatment. This cell-culture system is useful for further studies on the role of GGT in carcinogenesis. (Author abstract) (26 Refs)

33. GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY OF TRANSFORMED RAT HEPATOCYTES (MEETING ABSTRACT).

Jacobsen LB, Putnam JE, Matyas GR, Morre DM, Morre DJ
Department of Biological Sciences and Foods and Nutrition, Purdue University, W. Lafayette, IN, 47907
In Vitro; 18(3,part2):285 1982

Although many in vitro markers are being used to identify cultured fibroblasts as either normal or neoplastically transformed, there are no uniform criteria for epithelial cells. Furthermore, markers vary for each epithelium. Two frequently used markers for transformation of rat hepatocytes are growth in soft agar, and increased gamma-glutamyl transpeptidase (GGT) activity. Cell lines developed in this laboratory from a carcinogen-induced hepatocellular carcinoma were analyzed for these markers. The PCCL-H2 cell line produces poorly to moderately differentiated hepatocellular carcinomas in vivo, is strongly GGT positive, but less than 15% of the cells from colonies in soft agar. On the other hand the PCCL-H10 line, derived from a tumor which developed following subcutaneous inoculation of PCCL-H2 cells, produces poorly differentiated neoplasms, is weakly GGT positive, yet over 50% form colonies in soft agar. Sublines of the PCCL-H10 soft agar colonies lack the expected GGT activity, yet over 70% form colonies in soft agar. These results suggest that GGT activity is not a reliable transformation marker and should be used in combination with other in vitro markers to evaluate the transformed phenotype of rat liver cells. (no Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

34. BIOCHEMICAL AND IMMUNOCYTOCHEMICAL ANALYSIS OF THE INTERMEDIATE FILAMENT CYTOSKELETON IN HUMAN HEPATOCELLULAR CARCINOMAS AND IN HEPATIC NEOPLASTIC NODULES OF MICE.

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Lab Invest; 46(6):384-596 1982

Cytoskeletons enriched in intermediate-sized filaments were isolated from neoplastic and non-neoplastic hepatocytes of murine and human liver as well as from human cholangiocellular carcinoma, using extractions in high salt buffers and Triton X-100, and were analyzed by immunofluorescence microscopy and by one- and two-dimensional gel electrophoresis. This study presents the first comparison of the cytoskeletal pattern of a human nonepidermal tissue and the corresponding carcinoma. Despite some minor but significant differences of electrophoretic mobilities of the major cytokeratin polypeptides present in rodent and human liver, their similar pattern on two-dimensional gel electrophoresis suggests a tissue or cell type-specific pattern in both species. Moreover, the results show that not only cytokeratins are continued to be expressed when hepatocytes become neoplastic but also that the hepatocyte-specific pattern of major cytokeratin polypeptides is maintained. (Author abstract) (45 Refs)

35. ISOLATION AND CHARACTERIZATION OF A NEW FUCOGANGLIOSIDE ACCUMULATED IN PRECANCEROUS RAT LIVER AND IN RAT HEPATOMA INDUCED BY N-2-ACETYLAMINOFLUORENE.

Holmes EH, Hakomori SI
Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Biol Chem; 257(13):7698-7703 1982

A novel fucoganglioside has been found to be accumulated in the liver of rats fed N-2-acetylaminofluorene before development of hepatoma. This new fucoganglioside persisted in hepatoma in vivo but was completely absent in normal rat liver as well as in livers of rats fed the nonhepatic carcinogen, acetylaminophenanthrene, and a tumor promoter, trichloro-2,2-bis-(chlorophenyl)ethane. The ganglioside was isolated by high performance liquid chromatography and the structure was determined by methylation analysis, sequential degradation by various exoglycosidases, and by direct probe mass spectrometry of the permethylated derivative. This ganglioside, present in precancerous liver and in hepatoma in vivo, was identified as having a new structure with a substitution identical with blood group B determinant. A second fucoganglioside was detected in lower quantity in precancerous liver and in hepatoma in vivo but not in control tissue. This ganglioside co-migrated with the fucoganglioside isolated from H-35 hepatoma cells in vitro whose structure was identified as fucosylated GM1 ganglioside (Fucalpha1 to 2Galbeta1 to 4GalNAcbeta1 to 4 [NeuAcalpha2 to 3]Galbeta1 to 4Glcbeta1 to 1Cer). The results indicate that synthesis of new fucolipids is already induced at an early stage during the process of chemical carcinogenesis in rat liver which could be a unique membrane marker for diagnosis and therapy of a hepatoma and its premalignancy. (Author abstract) (45 Refs)

36. STUDY OF THERMOINDUCED STRUCTURAL CHANGES IN MEMBRANES AND LIPIDS OF LYSOSOMES DURING EXPERIMENTAL CARCINOGENESIS.

Kotrikadze NG, Gabuniia GD, Dzhishkariani OS, Tsartsidze MA, Lomsadze BA
State Univ., Tbilisi, USSR
Biofizika; 27(3):454-457 1982

Structural changes in the membranes and lipids of lysosomes isolated from normal liver, liver of tumor-bearing rats, and Walker 256 carcinosarcoma were studied by means of spin probes. Analysis of rotational correlation for the spin probes showed that the structural transitions in the lysosomes of the normal liver occurred at 34-64 C, compared with 30 C for the from the liver of tumor-bearing rats and 28-40 C for those from the tumor. (8 Refs) (In RUS)

37. EARLY BIOCHEMICAL EVENTS COMPARING 2-ACETYLAMINOFLUORENE HEPATOCARCINOGENESIS AND 4-ACETAMIDOPHENOL HEPATOTOXICITY IN THE RAT (MEETING ABSTRACT).

Sawick DP, Elliott WL, DeFrees SA, Heinstein P, Cassady JM, Morre DJ
Department of Medicinal Chemistry, Purdue University, West Lafayette, IN, 47907
Proc Am Assoc Cancer Res; 23:209 1982

This study compares pyrimidine biosynthetic alterations of dihydroorotate dehydrogenase, uridine-5'-diphosphate kinase (UDP kinase), cytidine-5'triphosphate synthetase (CTP synthetase); and gamma-glutamyl transpeptidase in livers of rats fed 0.025% of the hepatocarcinogen 2-acetylaminofluorene (AAF) or 1.87% of the hepatotoxin, 4-acetamidophenol (AAP) in their diets. Results showed that within three days of AAF feeding dihydroorotate dehydrogenase specific activity was decreased to 0.6 of control while UDP kinase was increased 2.7-fold. After 14 days, a 2-fold increase in the activity of CTP synthetase was observed and by day 21 gamma-glutamyl transpeptidase specific activity was increased 8-fold. Histologically, acute centrilobular necrosis was observed in the livers of AAP fed animals. Yet no biochemical alterations resembling those induced by AAF were obtained. Dithydroorotate dehydrogenase specific activity was increased slightly as a result of hepatotoxicity but was decreased in hepatocarcinogenesis. UDP kinase and gamma-glutamyl transpeptidase specific activities were unaffected by AAP. CTP synthetase specific activity, elevated in hepatocarcinogenesis, was decreased slightly in hepatoxicity. (no Refs)

38. CHANGES OF TRYPTOPHAN PYRROLASE ACTIVITY IN LIVER OF RATS SUBJECTED TO SINGLE INJECTION OF HEPATOCARCINOGEN 4-DIMETHYL-AMINOAZOBENZENE AND ITS NONCARCINOGENIC ANALOG.

Chernyshova MD, Medvedeva ND
Lab. Cytology Tumor Growth, Inst. Cytology, Leningrad, USSR
Tsitologiia; 24(5):615-617 1982

The effect of single ip injection of hepatocarcinogen 4-dimethyl-aminoazobenzene (DAB) and its noncarcinogenic analog 4-diethyl-aminoazobenzene (DEAB) on activity of liver tryptophan pyrrolase (TP) was studied in random-bred albino rats. Both DAB and DEAB at 250 mg/g produced short-term elevation of TP activity. Progressive decrease of TP activity was observed within 4-12 days after administration. The decrease of TP activity was associated with progressive decrease of the number of differentiated cells in the liver. (14 Refs) (In RUS)

39. SOME BIOCHEMICAL PROPERTIES OF THE PRENEOPLASTIC ANTIGEN IN RAT LIVER HYPERPLASTIC NODULES.

Ogino MA, Okita K, Tsubota W, Numa Y, Kodama T, Takemoto T
First Div., Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, 1144 Kogushi, Ube 755, Japan
Gan; 73(3):349-353 1982

The biochemical properties of preneoplastic antigen (PN antigen) were investigated in order to resolve inconsistencies in previous reports. First of all, expoxide hydrase was purified biochemically from the liver of phenobarbital-treated rats and anti epoxide hydrase serum was prepared in rabbits. Immunochemically, in Ouchterlony double diffusion, PN antigen had the same antigenicity as epoxide hydrase. From an immunoprecipitation study using sodium dodecyl sulfate-polyacrylamide gel electrophoresis and crossed immunoelectrophoresis, it was found that PN antigen may be composed of epoxide hydrase and at least one more protein (mol wt 27,000). However, the biochemical and biological properties of the protein binding to epoxide hydrase were not determined. The existence of PN antigen (epoxide hydrase and its binding protein) may be associated with microsomal membrane alterations during chemical carcinogenesis. (Author abstract) (14 Refs)

40. INDUCTION OF SPERMIDINE N(1)-ACETYLTRANSFERASE BY DIALKYLNITROSAMINES.

Matsui I, Pegg AE
Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Cancer Res; 42(8):2990-2995 1982

Treatment of rats with dimethylnitrosamine (30 mg/kg) or diethylnitrosamine (200 mg/kg) produced a rapid increase in the activity of spermidine N1-acetyltransferase which peaked at values seven-fold greater than did control at 48 hr after exposure. This increase led to a small accumulation of N1-acetylspermidine in the liver but produced a more striking effect on putrescine which increased 30-to 40-fold after 2 days. Most of this increase appeared to be due to the conversion of N1-acetylspermidine into putrescine which is catalyzed by polyamine oxidase. Treatment with the nitrosamines also increased the conversion of spermine into spermidine which replaced the spermidine converted into putrescine. Spermine levels were therefore significantly depressed by treatment with these carcinogens. These results indicate that these hepatocarcinogens bring about an increase in putrescine and in the spermidine/spermine ratio in the liver not only by enhancement of ornithine decarboxylase but also by induction of the spermidine N1-acetyltransferase activity which is the rate-limiting step in the acetylase-oxidase pathway for interconversion of the polyamines. (Author abstract) (35 Refs)

41. CELL SPECIFICITY IN HEPATOCARCINOGENESIS: PREFERENTIAL ACCUMULATION OF O(6)-METHYLGUANINE IN TARGET CELL DNA DURING CONTINUOUS EXPOSURE OF RATS TO 1,2-DIMETHYLHYDRAZINE.

Bedell MA, Lewis JG, Billings K C, Swenberg JA
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3079-3083 1982

Concentrations of the major methylated DNA purines were determined in two liver cell populations of Fischer 344 rats during administration of 30 ppm 1,2-dimethylhydrazine (SDMH) in the drinking water for periods of up to 4 wk. Quantitation of 7-methylguanine and O6-methylguanine (O6MG) was achieved by highly sensitive optical methods following separation of DNA bases by high-performance liquid chromatography. Overall alkylation as indicated by the concentration of 7-methylguanine was near max in both hepatocytes and liver nonparenchymal cells by the third day of SDMH administration. Similar amounts of 7-methylguanine were present in the two liver cell populations at seven of nine time points during 4 wk of exposure. In contrast, dramatic differences in the cumulative concentrations of O6MG were seen in the two cell populations. Nonparenchymal cells accumulated O6MG during the first 8 days of exposure and had up to a 30-fold greater concentration of this product than did the corresponding hepatocytes. In the hepatocytes, a rapid decline in O6MG concentration was observed between 1 and 3 days of exposure to SDMH. Thereafter, only low levels of this promutagenic lesion were present in hepatocytes. Exposure of rats to the same regimen of SDMH for up to 10 mo caused angiosarcomas in the livers of over 90% of the animals, while hepatocellular carcinomas occurred in only 40%. Thus, a strong correlation exists between the inability to repair O6MG and cell specificity for carcinogenesis. (Author abstract) (50 Refs)

42. INCREASED AMOUNTS OF DOUBLE-STRANDED RNA IN THE CYTOPLASM OF RAT LIVER FOLLOWING TREATMENT WITH CARCINOGENS.

Clawson GA, Smuckler EA
(c/o Smuckler) Dept. Pathology, HSW547, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(8):3228-3231 1982

Cytoplasmic RNA was isolated from control rats or at 48 hr following carcinogen administration. A significant quantity (0.6%) of double-stranded RNA was present in control preparations, as assessed by digestion with RNase III. Following carcinogen treatment of rats, this percentage increased significantly. The results suggest that the altered transport of repetitive sequences which is induced by carcinogen treatment involves alterations in the metabolism of double-stranded RNA sequences. (Author abstract) (60 Refs)

REVIEWS AND OTHER RELATED STUDIES

43. PRIMARY HEPATOCELLULAR CARCINOMA: PRESENT STATE OF THE DISEASE AND PROSPECTS FOR THE FUTURE.

Oon CJ, Friedman MA
(c/o Friedman) Cancer Res. Inst., Univ. California, 1282-M, San Francisco, CA, 94143
Cancer Chemother Pharmacol; 8(2):231-235 1982

The pathobiology, epidemiology and current techniques of therapy of primary hepatocellular carcinoma (PHC) are reviewed. PHC is an almost uniformly fatal primary hepatic malignancy responsible for the death of an estimated one million people annually. Incidence ranges from 2-104/100,000 (age-standardized to world population). The regenerating, damaged liver appears to be most susceptible to this malignancy, and great interest has been focused upon the relationship between hepatitis B infection and PHC. In particular areas of the world, ingestion of mycotoxins and various nutritional factors may play a role in etiology of PHC. Race has been correlated with environmental factors in some epidemiological studies of PHC incidence. Contaminated water supplies have also been associated with increased incidence of PHC. PHC appears to be more prevalent in males than in females. In experimental animals various steroid hormones promote tumor development in chemically induced PHC. How this may be related to the ingestion of oral contraceptives by human females remains clear. Conventional surgical and radiological approaches to eradication of PHC have proven unsatisfactory. The single most effective drug appears to be adriamycin, which results in response rates of 35-50% and improved survival when used in appropriate patients. Combinations of chemotherapeutic drugs and radiation have yielded better response rates. New approaches toward prevention and treatment of PHC are discussed. (37 Refs)

44. ALCOHOL AND CARCINOGENESIS.

Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982

The relationship between alcoholism and carcinogenesis is reviewed. Alcohol has been linked to increased incidences of cancers of the oropharynx, larynx, esophagus, liver, and probably the pancreas and rectum. Beverages with high alcohol content present greater risks than wine or beer. Alcoholism has a synergistic effect on carcinogenesis caused by smoking. Cirrhosis of the liver caused by alcoholism is important as a precancerous condition. Beer consumption increases the risk of pancreatic cancer; chronic pancreatitis is not involved as an intermediate stage. Beer consumption also increases the incidence of rectal cancer. Other cancers possibly related to alcohol abuse include carcinomas of the kidney, prostate, bladder, breast, and thyroid. Animal studies indicate that alcohol by itself is not carcinogenic. Alcohol apparently has a cocarcinogenic effect. Alcohol may induce specific enzyme systems that interact with carcinogens. It may be active in either the initiation phase, the promotion phase, or both. In the gastrointestinal tract it may induce carcinogenesis by local effects. Systemic effects include alterations in hormonal and immune functions, as well as in the actions of vitamins and minerals. In addition, alcoholic beverages contain a number of carcinogenic substances. (179 Refs) (In GER)

45. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.

Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982

A review of hepatic diseases concerning the use of oral contraceptives shows a considerable increase in the incidence of benign hepatic tumors and precancerous conditions (adenoma, focal nodular hyperplasia and mixed benign tumors) since the introduction of oral contraceptives. Seventeen cases of malignant hepatic tumors (hepatocellular carcinoma in 16 and mixed tumor in 1) following the use of oral contraceptives for 1-11 yr were found in the literature. (82 Refs) (In GER)

46. HEPATIC CIRCULATION IN HEALTH AND DISEASE.

Lautt WW
Dept. Physiology, Coll. Medicine, Univ. Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada
Hepatic Circulation in Health and Disease. New York, Raven Press, 382 pp., 1981.

Recent methodological, physiological, and clinical advances in the study of hepatic circulation are reviewed. Gross and microscopic approaches that have led to major discoveries are described. Current concepts of control of blood flow, blood vol, and exchange between parenchymal cells and plasma are presented. The clinical orientation is approached applying basic knowledge to clinical problems and using clinical data to evaluate and direct basic research areas. Transilluminated liver in microvascular methods, a combined method for the evaluation of the splanchnic circulation in rats, tracer behavior in the hepatic microcirculation, hepatic plethysmography, applicable human methodology in hepatic circulation, review of methods and results of scanning electron microscopy of casts of hepatic microvessels, and quantitative morphological assessment of the sinusoids of the hepatic acinus are presented. Current concepts of hepatic lymph, hepatic fluid exchange, acinus as the microvascular unit of the liver, mobilization of blood from the splanchnic circulation, role and control of the hepatic artery, and the fetal and neonatal hepatic circulation are discussed. Pathology of the hepatic vasculature including hepatic vascular tumors, an experimental approach to liver carcinogenesis, the congested liver, portal hypertension, the possible role of liver oxygen demand and hepatocyte enlargement in the pathogenesis of alcoholic liver disease are described. (792 Refs)

47. BENIGN HEPATIC TUMORS.

Pollice L, Resta L, Russo S
Istituto di anatomia e istologia patologica, Universita degli Studi di Bari, Bari, Italy
Pathologica; 74(1029):1-22 1982

Benign hepatic tumors are reviewed on the basis of a new histological classification. The benign tumors of the liver include hepatocellular tumors (focal nodular hyperplasia, hepatocellular adenoma), cholangiocellular tumors (cholangioadenoma, biliary cystadenoma), vascular tumors (capillary, cavernous or sclerosing) hemangiomas, infantile hemangioendothelioma, mesenchymal hamartoma, rare mesenchymal tumors (fibroma,leiomyoma, myxoma and lymphangioma), and teratoma. The relationship between the use of oral contraceptives and focal nodular hyperplasia, hepatocellular adenoma and hepatic peliosis is discussed. (66 Refs) (In ITA)

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Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
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RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982
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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
Beach RS, Gershwin ME, Hurley LS
Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
Magnus K
The Cancer Registry Norway, Montebello, Oslo 3, Norway
Trends in Cancer Incidence: Causes and Practical Implications, Proceedings of a Symposium held Oslo, Norway, 6-7 August 1980. Washington, D. C., Hemisphere Publishing Corporation, 446 pp., 1982.

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

8. QUANTIFICATION OF OCCUPATIONAL CANCER.
Peto R, Schneiderman M
Nuffield Dept. Clinical Medicine, Radcliffe Infirmary, Univ. Oxford, Oxford, England
Banbury Rep (9): 756 pp., 1981.

9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
Sch. Medicine, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814
JOM; 24(7):526-530 1982

10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.
Madsen ES, Nielsen PA, Pedersen JC
(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
Ugeskr Laeger; 144(23):1719-1721 1982
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11. AIR POLLUTION AS A RISK FACTOR IN LUNG CANCER.
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Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, 2211 Main St., Buffalo, NY, 14214
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12. INHALATION CARCINOGENESIS: AN OVERVIEW.
Chretien J
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Recent Results Cancer Res; 82:1-10 1982

13. THE NITROSAMINE HAZARD.
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Ear Nose Throat J; 61(7):407-414 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.
Weinberg RA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Adv Cancer Res; 36:149-163 1982

15. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.
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Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

16. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.
Fedorov NA
Central Res. Inst. Hematology and Blood Transfusion, Moscow, USSR
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17. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.
Harguindey S
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Med Pediatr Oncol; 10(3):217-236 1982

MODIFICATION OF CARCINOGENESIS

18. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.
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Inst. Biochemistry, German Cancer Res. Center, Heiodelberg, W. Germany
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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

19. AVIAN LEUKEMIA VIRUSES: ONCOGENESES AND GENOME STRUCTURE.
Graf T, Stehelin D
Inst. Virology, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
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20. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.
Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
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J Chronic Dis; 35(7):581-600 1982

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Sivak A
(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 98(3):377-387 1982

23. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.
Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
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25. THE PHYSIOLOGICAL IMPORTANCE OF THE COLONIC MICROFLORA.
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Dept. Germfree Res., Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Scand J Gastroenterol [Suppl]; 17(77):117-131 1982

26. AN ASSESSMENT OF THE ROLE OF MICRODOSIMETRY IN RADIOBIOLOGY.
Goodhead DT
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Cohen J, Cullen JW, Martin LR
Sch. Social Welfare, Univ. California, Los Angeles, Los Angeles, CA
Psychosocial Aspects of Cancer. New York, Raven Press, 320 pp., 1982.

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Liver

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EPIDEMIOLOGY AND ETIOLOGY OF HUMAN LIVER CANCER AND RELATED DISEASE

1. THE EPIDEMIOLOGY OF CANCER IN CHINA.

Armstrong B
Dept. Medicine, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia, Australia
World Health Forum; 3(1):95-101 1982

Epidemiology of cancer in China based on a retrospective survey of cancer mortality with additional data on the main cancer sites is reviewed. A total of 18,439,072 deaths were surveyed and 1,868,310 (10.1-11.3% in males and 8.8% in females) were attributed to cancer. The highest level of diagnosis and treatment and the best available criterion for the diagnosis of cancer are summarized. For all sites of cancer together the estimated mortality rates in China were 119.6/100,000 for males and 80.7/100,000 for females, adjusted to age distribution of the 'world' population. Among countries reporting mortality by site of cancer, China has the highest mortality from esophageal cancer with annual rates of 31.7/10,000 in males and 15.9/100,000 in females. Cancer of the stomach is the most common

HE 20. 3173/2:

form of cancer leading to death in China. The mortality rates are 32.4 and 15.9/100,000 in males and females, respectively. The rates are substantially lower than those in Japan. Liver cancer (presumed primary) is the third more important cancer as a cause of death in China and accounts for [illegible]% of all cancer deaths. Mortality rates of the cancer of the cervix are generally higher in the rural than in urban areas. An unusual feature of the high rate of lung cancer in Chinese women, particularly Cantonese women, is the relatively high proportion of the tumors which are adenocarcinomas. The county with highest rates of large bowel cancer is an area of endemic schistosomiasis in Zhajiang province. The geographic distribution of nasopharyngeal cancer within China is quite remarkable, with a very high incidence area centered on Guandong province in the south. (11 Refs)

2. A PROPORTIONATE MORTALITY STUDY OF AN OIL, CHEMICAL AND ATOMIC WORKERS LOCAL IN TEXAS CITY, TEXAS.

Reeve GR, Thomas TL, Kelly VF, Waxweiler RJ, Itaya S
Biometry Section, Industrywide Studies Branch, Natl. Inst. for Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, OH, 45226
Ann NY Acad Sci; 381:54-61 1982

A proportionate mortality ratio (PMR) study was conducted of deceased members of the Oil, Chemical and Atomic Workers Union in Texas City, Texas in order to determine whether unusual patterns of cancer mortality exist in petrochemical plants and refineries. A total of 264 white union members who died after 1947 were included in the study, and two refineries (A and B) were analyzed in depth. In Refinery A, the PMR for nonmotor vehicle accidents was elevated (12 deaths observed vs 7.36 expected) and that for all cancer was only slightly elevated (1.18). However, excess deaths from skin cancer (PMR = 7.88), brain and CNS neoplasms (4 observed vs 1.57 expected), kidney cancer (2 observed vs 0.84 expected), and liver cancer (3 observed vs 0.64 expected) were observed. In Refinery B, excess deaths from lung cancer (6 observed vs 3.86 expected; not statistically significant) and hematopoietic and lymphatic cancer (4 observed vs 1.22 expected) were observed. Thus, deaths due to skin, brain, liver, and kidney cancer at Refinery A and deaths due to hematopoietic and lymphatic cancer at Refinery B were proportionately in excess. The relative excess of melanoma deaths observed at Refinery A appears to represent an occupationally related health problem. The relative excess of other cancer deaths at these refineries warrant further study. (18 Refs)

3. PRIMARY HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS.

Blumberg BS, London WT
Dept. Medicine, Univ. Pennsylvania, Philadelphia, PA
Curr Probl Cancer; 6(12):1-23 1982

The history, pathobiology, prevention and etiology of hepatocellular carcinoma (HPC) associated with hepatitis B virus (HBV)-infection are reviewed. There is now substantial evidence to support the hypothesis that persistent HBV infection is required for the development of PHC. Prevention of infection with HBV will result in prevention of most cases of HBV. Strategies of primary prevention, intrafamily transmission, insect transmission, and a cellular model for primary hepatocellular carcinoma are among other topics discussed. The proposed model suggests an approach to cancer therapy different from that usually used. While most conventional therapies are directed toward the total destruction of cancer cells, with the side-effect of normal tissue damage, the model suggests that the viability of infected noncancerous cells should be enhanced so that their numbers relative to those cells with integrated HBV DNA will increase and thereby prevent the continued growth of tumors. (35 Refs)

4. THE RELATIONSHIP BETWEEN HEPATITIS B ANTIGEN AND PRIMARY LIVER CANCER.

Zhang F
Anti-epidemic Station, Manning District, Guarjxi Province, Nanning, People's Republic of China
Zhonghua Liuxingbingxue Zazhi; 3(1):49-52 1982

Two villages, S and Y, only 1,000 feet apart were investigated to determine why they showed a drastically different incidence of primary hepatoma. S had an incidence of 328.73 per 100,000 persons, whereas Y had none in 15 years. The incidence had a remarkable familial aggregation phenomena. Among 20 persons who died, 15 were from 7 families with the remaining 5 also being related to the 7 families. Natural conditions of the villages, living conditions, customs, cultures, and foods consumed were very similar in both villages. No significant differences were found in the content of aflatoxin B1 in the food of both villages. A significantly different distribution of hepatitis B-related events was found. The number of hepatitis B antigen carriers in S was clearly higher than that in Y (p less than 0.05), and more people in S than in Y had a high level of anti-hepatitis B antibody (p less than 0.001). explaining why hepatitis B viral infection rate was greatly higher in S than in Y. The rate of enlarged liver and the rate of viral hepatitis (70% were hepatitis B) were higher in S than in Y. However, no significant differences were seen between the two villages in the rate of liver function abnormality, which was found to be 42.8% for S and 51.12% for Y. Further investigation is needed to clarify these findings, which support the assumption that the hepatitis B antigen is closely related to the incidence of hepatoma. (7 Refs) (In CHI)

5. THE ASSOCIATION OF PRIMARY HEPATOCELLULAR CARCINOMA (PHC) WITH HBSAG POSITIVITY IN ASIAN PATIENTS ON HORMONAL CONTRACEPTIVE AGENTS IN SINGAPORE (MEETING ABSTRACT).

Oon CJ, Tsakok M, Singh R
University Department of Medicine, Singapore General Hospital, Singapore, Singapore
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Between 1979 and 1981 an ongoing prospective study was made on 236 female individuals on hormonal contraceptive agents (HCA). The objective was to determine the relationship between HCA and incidence of PHC in HCA takers and nontakers in an environment where the natural hepatitis B carrier rate in adult asymptomatic females was about 8% (by radioimmunoassay). Patients' sera were tested for alpha-fetoprotein (AFP) by CIE which in our laboratories has a detection limit of 80 ng/ml. Other tests included alpha 1 antitrypsin, Hepatitis B surface antigen (AUSRIA-II), anti-Hepatitis B core (anti-HBc) antigen (CORAB). The age group of study was 21-51 yrs, median 32 yrs; 3/236 (1.3%) HCA had PHC. These were 3 Chinese women between the ages of 26-29 yrs. The overall annual age specific incidence rates for PHC in Singapore for females aged 25-29 yrs is 0.172 per 100,000. Also 1,000 matched females non-HCA group showed no evidence of PHC over this period of study. Twenty-four HCA patients were HBsAg positive. All 3 PHC patients (13%) were HBsAg, anti-HBc positive. No PHC were seen in the other races - Malays (16), Indians (11) and others (3). One hundred and twelve of 236 (48%) were anti-HBc positive. The HCA taken were Nordette 85, Microgynon 14, Eugynon 36, Neogynon 26, Ovral 26, Gynovlar 6, Ovalen 2, Anovlar 10, New Lyndiol 10, Norethisterone 1, Lyndiol 1, Depoprovera 3. Ovral, Anovlar, Gynovlar and Ovalen were the HCA used by the PHC patients. Chinese females who are HBsAg positive appear to be at higher risk of having PHC than HBsAg negative females on HCA. (no Refs)

6. HUMAN LIVER NEOPLASIA AND STEROID EXPOSURE (MEETING ABSTRACT).

Barrows GH, Christopherson WM
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The authors have examined material from over 250 cases of steroid related liver tumors. Two distinct tumor types comprised the majority of benign tumors in this series. Focal nodular hyperplasia (55%) occurred in women with an average age of 32.3 years and an average steroid exposure of 74.7 months. Hepatocellular adenoma accounted for 40% of patients with an average age of 30.2 years, and exposure of 79.6 months. About 20% of patients with benign neoplasms had multiple tumors. Mortality among patients with benign tumor was 4.2% with a statistically significant increase in mortality from liver rupture associated with hepatocellular adenoma. There were 23 women with hepatocellular carcinoma occurring in non-cirrhotic livers, and a majority had a history of steroid usage. The average age of patients with malignant tumors was 30.6 years. Unlike the 'hepatocellular carcinomas:' reported in males taking anabolic androgenic steroids, the tumors in females had a high rate of metastasis to a variety of organs. (no Refs)

7. IS DYEING OF BAIT A CARCINOGENIC HAZARD FOR ANGLERS AND THEIR SUPPLIERS? (MEETING ABSTRACT).

Searie CE, Teale J
Department of Cancer Studies, The Medical School, Birmingham B15 2TJ, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Chrysoidine (2,4-diaminoazobenzene), once used as a food dye, induced liver tumors in most male and female mice when fed at 0.2% in the diet, and it was the most active of some azo dyes and reduction products tested for mutagenicity in Salmonella typhimurium TA 1538. Nevertheless it is currently in widespread use for dyeing maggots for use as bait by anglers, for which purpose the hydrochloride is mixed with maggots by anglers' suppliers shortly before sale. This causes considerable long-lasting staining of the hands of shop staff and, to a lesser extent, of the very many anglers who use the bait, often from an early age. A Midlands dealer, who uses 14 kg of chrysoidine HCl annually, became anxious about its safety and informed us of 3 angling acquaintances who had developed bladder tumors. The early ages of presentation -2 were under 40- would suggest a possible 'occupational' origin, but none had worked in the chemical or rubber industries. Some other dyes, including the carcinogen auramine, have also been used but apparently with lesser problems of contamination. (2 Refs)

TUMOR INDUCTION IN ANIMALS

8. INDUCTION OF CARCINOMA OF GALLBLADDER IN HAMSTERS BY INSERTION OF METHYLCHOLANTHRENE BEESWAX PELLETS.

Suzuki A, Watanabe M, Takahashi T
Dept. Surgery, Koto General Hosp., Akita, 018-16, Japan
Jpn J Surg; 12(3):227-228 1982

Successful induction of gallbladder cancer in female hamsters is reported. The animals were subjected to insertion of a pellet into the gallbladder. The pellet contained either beeswax alone (B group) or beeswax mixed with methylcholanthrene (MC-B group). The animals were sacrificed 170-201 days (B group) or 145-226 days (MC-B group) after insertion. Gallbladder carcinomas were observed in 9/23 hamsters in MC-B group and in 0/32 hamsters in B group. Dysplasia of the gallbladder epithelium was detected in three hamsters in MC-B group and in four hamsters in B group. (3 Refs)

9. HEPATOTOXICITY AND TUMORIGENICITY OF HEXACHLOROBENZE (HCB) IN SYRIAN GOLDEN HAMSTERS (H) AFTER SUBCHRONIC ADMINISTRATION (MEETING ABSTRACT).

Lambrecht RW, Erturk E, Grunden E, Headley DB, Morris CR, Peters HA, Bryan GT
University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Fed Proc; 41(3):329 1982

HCB, a rodent carcinogen, is a by-product of chlorinated hydrocarbon synthesis and used as a fungicide. It was fed to both sexes of H at doses of 0, 200, and 400 ppm for 90 days. On the 91st day, 25/50 H from each group were killed, and histologically examined. The remaining 25 H were fed HCB-free diet and sacrificed at 6-week intervals through day 361. Growth and food consumption did not differ between control and exposed H. Liver was the most severely involved organ exhibiting a variety of precirrhotic (PC) and cirrhotic (C) lesions, bile-duct hyperplasia (BDH), and hepatomas (HEP). (no Refs)

10. THE COMPARATIVE TOXICITIES AND CARCINOGENICITIES OF BENZIDINE AND DIRECT BLUE 6 IN RATS (MEETING ABSTRACT).

Mennear JH, Gupta BN
National Toxicology Program, National Institute of Environmental Health Services, Research Triangle Park, NC, 27709
Toxicologist; 2(1):35 1982

Direct Blue 6, a bisazobiphenyl dye known to be metabolized to benzidine (B) produces hepatocellular carcinoma when fed to rats at dietary concentrations of 1500 and 3000 ppm. The rapid onset of carcinoma (4 weeks) suggested that the effect might be mediated through mechanisms other than simple metabolism to B. The objective of the present study was to compare the potencies of the dye and B with respect to general toxicity and carcinogenicity. Groups of 20 female F344 rats were exposed to drinking water containing either B-2HCl (100-400 ppm) or the dye (500-2000 ppm) for up to 90 days. The concentrations of B were selected to be equivalent to B exposure if dye treated rats completely metabolized the chemical. Based on water consumption, the average daily doses of B were 10, 21, 28, 31 mg/kg while the B equivalents of the dye consumptions were 13, 22, 30 and 37 mg/kg/day. All rats exposed to the two highest doses of B died within 9 weeks while only 6 rats exposed to the high dye concentration died during the study. Among rats surviving to terminal sacrifice, both chemicals produced dose-related increases in serum gamma glutamyl transpeptidase with the magnitude of effect produced by the 21 mg/kg/day dose of B being similar to that produced by the highest dose of the dye. Additional dose-related effects produced by both chemicals included: thymic involution, increased liver weights, and grossly observable hepatic nodules. Hepatocellular carcinoma was diagnosed in some rats that died after receiving 28 mg/kg/day of B for up to 9 weeks. (no Refs)

11. SEX STEROID HORMONES LEVELS AND TESTICULAR ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE.

Lafaurie M, Aussel C, Castelli D, Krebs B, Stora C

INSERM U 210 (Laboratoire d'Histologie et d'Immunologie), 06034 Nice, France

Res Commun Chem Pathol Pharmacol; 37(1):49-63 1982

During hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The testes present a reduced activity which is evidenced by a decreased spermatogenetic activity accompanied by a drastic decrease of the plasma testosterone level. In contrast, plasma progesterone and estradiol-17beta levels were not modified despite the 80 fold augmentation of alpha-fetoprotein, an estrogen binding protein synthesized during liver carcinogenesis. (Author abstract) (27 Refs)

12. DEVELOPMENT OF HEPATOCELLULAR AND CHOLANGIOCELLULAR NEOPLASMS IN THE LIVERS OF MALE AND FEMALE SPRAGUE-DAWLEY RATS AFTER CHRONIC ADMINISTRATION OF AROCLOR 1260 (MEETING ABSTRACT).

Weltman RH, Norback DH

William S. Middleton Memorial Veterans Administration Hospital, Madison, WI

Fed Proc; 41(3):446 1982

Neoplastic nodules (NN), trabecular hepatocellular carcinoma (THC), mixed hepatocholangiocellular carcinoma (MHC), simple cholangioma (SC), cystic cholangioma (CC), and cholangiofibrosis (CF) occurred in the Sprague-Dawley rat after chronic dietary administration of Aroclor 1260 (100ppm in the diet for 16 months followed by 50ppm for 8 months and control diet for 5 months). A low incidence of spontaneous hepatocellular and cholangiocellular lesions occurred in this strain of rat. In 81 rats (32 male and 49 female), examined during the 18th through the 29th month of this study, only one hepatocellular tumor and an incidence of 6% SC, 2% CC and 4% CF occurred in the rat population fed a control diet. Hepatocellular tumors developed in 95% of the 47 female rats (4% NN only, 51% HCC and 41% MHC), whereas hepatocellular tumors developed in 15% of the 46 male rats (11% NN only and 4% HCC). Within the female rat group, SC developed in 45%, CC in 10%, and CF in 15%. Within the male rat group, SC developed in 31%, CC in 4% and CF in 2%. Hepatocellular and cholangiocellular neoplasms persisted during the 5 month period of a conrol diet. We propose that Aroclor 1260 acts as a complete carcinogen in the liver having both initiating and promoting activity. (no Refs)

13. LACK OF HEPATOGENOTOXICITY OF ORAL CONTRACEPTIVE STEROIDS.

Yager JD, Fifield DS

Dept. Environmental Medicine, New York Univ. Medical School, 550 First Ave., New York, NY, 10016

Carcinogenesis; 3(6):625-628 1982

The objective of the present study was to determine whether mestranol could initiate hepatocarcinogenesis and whether various gonadal steroids have detectable hepatogenotoxic potential. To test for initiation potential, female, Sprague-Dawley rats were partially hepatectomized and intubated with mestranol (100 or 500 mg/kg) 24 hr later. Twenty-four hr after treatment all rats were transferred to diet containing 0.05% phenobarbital to promote hepatocytes initiated by mestranol treatment. Four mo later an analysis of putative preneoplastic gamma glutamyl transpeptidase positive foci indicated that mestranol did not cause a significant increase in the number of such foci. Hepatogenotoxicity was assessed in two ways, first using alkaline elution to detect liver DNA damage after in vivo treatment with mestranol, and second by detection of DNA repair synthesis in primary cultures of hepatocytes treated with various oral contraceptive steroids. The results of both studies were negative. In conclusion, the oral contraceptive steroids do not exhibit strong initiating or genotoxic potential. (Author abstract) (21 Refs)

14. INCIDENCE AND TYPE OF TUMORS INDUCED BY ORAL DMBA IN NK CELL DEFICIENT C57B1 BG/BG MICE, +/BG LITTERMATES AND H-2 CONGENIC STRAINS OF B10 OF VARYING NK ACTIVITY (MEETING ABSTRACT).

Cochran AJ, Argov S, Karre K, Klein GO, Klein G

Pathology and Surgery, University of California, Los Angeles, CA

Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

To study the effect of the beige mutation on chemical carcinogenesis, 64 C57B1 bg/bg mice and 83 +/bg littermate controls received 5 weekly intragastric doses of DMBA (dimethylbenzanthracene). We examined the incidence and histological types of tumors that developed. By 165 days after first DMBA contact 18% of +/bg, and 31% of bg/bg mice developed tumors. Beige mice had a higher incidence of epithelial and non-epithelial tumors in cutaneous or subcutaneous sites. The incidence of lymphomas was similar in the groups but they appeared earlier in the beige. After 500 days 33 +/bg and 27 bg/bg mice were still alive, 60 of 83 +/bg animals (72%) and 47 of the 64 bg/bg (74%) having developed tumors. The beige group showed a higher incidence of non-thymic lymphomas, but the incidence of thymic lymphomas, cutaneous epithelial tumors and bile duct adenomas was similar in the two groups. In a continuing study of NK intact B10 (27), B10A (25), B10.BR (39), B10G (48) mice and NK cell deficient B10S congenic animals (30), squamous carcinomas have developed more frequently in B10S animals (B10S 8/30-27%) rest (11/139-8%). At present it looks as though both thymic and extra thymic lymphomas may also be of increased frequency in the B10S, NK deficient animals. (no Refs)

MODIFICATION OF HEPATOCARCINOGENESIS

15. QUANTITATIVE ANALYSIS OF INITIATING AND PROMOTING ACTIVITIES OF FIVE MYCOTOXINS IN LIVER CARCINOGENESIS.

Imaida K, Hirose M, Ogiso T, Kurata Y, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Cancer Lett; 16(2):137-143 1982

Initiating and promoting activities of several mycotoxins, citrinin (CIT), ochratoxin A (OTA), sterigmatocystin (STC), patulin (PAT), and (+)rugulosin (RUG), were examined in F344 rats using N-2-fluorenylacetamide. The animals were divided into four groups. Two groups were divided into five subgroups for tests on individual mycotoxins. Each subgroup consisted of 20 6-wk-old animals which were killed at wk 10 of the experiment. No foci were visible on the surface of the liver at the time of killing except in the group treated with STC. Significantly increased numbers of hyperplastic nodules (HN) were induced by administration of all mycotoxins examined in the initiating stage. OTA, STC, and PAT significantly increased the areas of HN as well as their numbers. When given in the promoting stage, OTA and STC significantly increased both the numbers and areas of HN, but RUG increased only the number of HN compared with those of the control group. Data showed that OTA, STC, and RUG had activity in both the initiating and promoting stage, whereas CIT and PAT exhibited only initiating activity. (20 Refs)

16. RESPONSE OF LIVER FOCI IN RATS TO HEPATIC TUMOR PROMOTERS (MEETING ABSTRACT).

Schulte-Hermann R, Timmermann-Trosiener I, Schuppler J
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

Foci of altered hepatocytes were induced by single doses of initiating hepatocarcinogens and visualized by various histochemical and morphological markers. DNA synthesis, measured by 3H-thymidine and autoradiography, as well as mitotic activity were found to be higher in the foci than in normal hepatocytes; several different tumor promoters (phenobarbital, gestagens, nafenopin, hexachlorocyclohexane) caused further increases in replicative activity of focal cells. Prolonged administration of promoters resulted in appearance of more and larger foci, which exhibited steady growth. Promoter withdrawal led to rapid reductions in size and number of foci. These studies show that the effect of liver tumor promoters is reversible under the conditions employed, as previously noted for skin tumor promoters. Furthermore, promoters seem to encourage growth of a subpopulation of foci that lack mechanisms limiting cell multiplication in normal liver and which depend on the sustained presence of the promoter for survival and/or expression of the specific phenotype of the focal hepatocyte. Finally mechanisms will be considered by which the promoters mentioned as well as other nonmutagenic compounds may produce liver tumors in experimental animals. (no Refs)

17. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).

Hill DL, Grubbs CJ
Southern Res. Inst., Box 3307-A, Birmingham, AL, 35255
Anticancer Res; 2(1/2):111-124 1982

Certain retinoids have prevented induction of cancer by carcinogens in the skin, mammary gland, and urinary bladder of experimental animals. In isolated experiments retinoids have also shown anticancer activity against esophageal, cervical, and hepatic cancers. No conclusive evidence of prophylactic activity against cancers of the lung or colon has been found. Retinoids have shown modest activity against those established cancers that are immunogenic. Retinoids apparently have antipromoting and general immunostimulative activities. (137 Refs)

18. DOSE-RESPONSE STUDIES ON THE INHIBITION OF EXPERIMENTAL MAMMARY, COLON, AND LIVER CARCINOGENESIS BY BUTYLATED HYDROXYTOLUENE (BHT) (MEETING ABSTRACT).

Cohen LA, Reddy BS, Williams GM, Furuya K, Maeura Y, Silverman J, Weisburger JH
Naylor Dana Institute, American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:358 1982

Phenolic antioxidants such as BHT inhibit carcinogenesis at several target organs including breast, colon, liver, lung, and stomach. We investigated (1) whether a dose response relationship exists between the tumor inhibiting effect and BHT level, and (2) whether the inhibiting is influenced by the dose of initiating carcinogen in three well-characterized model systems: the dimethyl-benz(a)anthracene (DMBA)-induced mammary carcinoma, the azoxymethane-induced colon carcinoma, and the 2-acetylaminofluorene (2-AAF)-induced hepatoearcinoma. Two appropriate doses of initiating carcinogen were used and BHT was fed in the diet at concentrations of 6000, 3000, 1000, and 300 ppm. In mammary carcinogenesis, tumor incidence was 75% and 55% and tumor multiplicity 2.5 and 1, respectively, at high (15 mg) and low (5 mg total) dose DMBA. With the high DMBA dose, tumor incidence and multiplicity were significantly inhibited only at the highest level of BHT. At low DMBA dose, tumor incidence and multiplicity were inhibited at all levels of BHT. In colon carcinogenesis, at the high dose of azoxymethane, inhibition as determined by endoscopy was evident at the two higher doses of BHT. In the liver model, 6 weeks of feeding 0.02% AAF produced 26 preneoplastic foci/cm2 liver, identified by resistance to iron accumulation. Concurrent feeding of BHT produced a dose-dependent inhibition of foci production. Thus, BHT exerts a dose-dependent inhibition of carcinogenesis in all three model systems. (no Refs)

19. LIVER TUMOURS AFTER SINGLE DOSE DIMETHYLNITROSAMINE, LOW AND HIGH PROTEIN DIET, AND PHENOBARBITONE.

McLean AE, Smith M, Driver HE
Lab. Toxicology, Dept. Clinical Pharmacology, Sch. Medicine, Univ. Coll. London, 5, University St., London WC1E 6JJ, England
Carcinogenesis; 3(6):707-709 1982

A single dose of 15 mg/kg dimethylnitrosamine given to rats at the time of switch from low to high protein diet is an effective initiator of hepatic tumor formation. With phenobarbitone as promoter, a high yield of liver tumors is produced. The switch from low to high protein diet may be a way of enhancing tumor initiation in many tissues. (Author abstract) (23 Refs)

20. THE INFLUENCE OF SEX, DOSE, TIME, AND CROSS ON NEOPLASIA IN MICE GIVEN BENZIDINE DIHYDROCHLORIDE.

Nelson CJ, Baetcke KP, Frith CH, Kodell RL, Schieferstein G
Dept. Health and Human Services, Food and Drug Admin, Natl. Center for Toxicological Res., Jefferson, AR, 72079
Toxicol Appl Pharmacol; 64(2):171-186 1982

Features of liver tumor development associated with exposure of mice to benzidine dihydrochloride (0, 30, 60, 120, 200, and 400 ppm in water) were studied. Half the mice (1,728) were obtained from mating C57BL/6JfC3Hf/Nctr females with BALB/cStCrLfC3Hf/Nctr males, and were called F-1 hybrids; another 1,728 mice were obtained by mating an F-1 hybrid inter se, and were called the monohybrid cross. Animal weight, water consumption, hepatic foci of cellular alterations and liver tumors, liver tumor dose-response relationship, survival time, time-to-tumor analysis, and other variables were monitored, usually at 40, 60, and 80 wk. Monohybrid males were more susceptible than F-1 hybrid males to the toxic effects of benzidine dihydrochloride as exhibited by weight loss. Monohybrid males also experienced considerable early mortality of unknown cause. F-1 and monohybrid animals were very similar for a number of dose-response relationships, including hepatic foci of cellular alterations, liver tumor incidence, liver tumor survival, and overall survival. There was a slight difference in liver tumor survival between F-1 and monohybrid females. Positive relationships between certain hepatic foci of cellular alterations and hepatocellular adenomas were suggested by the results for females, but not for males. The time required for death from liver tumors after initial tumor formation was not dependent on either sex or dose level of benzidine. The predominant benzidine-related cause of death was liver tumors, although females may have been affected by other unknown toxic factors. (28 Refs)

21. ASSESSMENT OF THE CAPACITY OF POLYBROMINATED BIPHENYLS TO SERVE AS PROMOTERS OF HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Jensen RK, Sleight SD, Goodman JI, Aust SD, Trosko JE
Department of Pathology, Michigan State University, East Lansing, MI, 48824
Toxicologist; 2(1):99 1982

Large doses of Firemaster (FM), a mixture of polybrominated biphenyls (PBB), cause hepatic cancer in rats. At noncytotoxic concentrations, FM and its major congener, 2,2',4,4',5-5'-hexabromobiphenyl (HBB) inhibit intercellular communication in vitro, a property associated with known tumor promoters. The purposes of this study were to assess the in vivo capacity of PBB to promote hepatocarcinogenesis and to evaluate the reliability of the in vitro assays. FM BP-6 and HBB were compared with phenobarbital (Pb), in a two-stage model for hepatocarcinogenesis devised by Pitot and associates. Female Sprague-Dawley rats weighing 200-250 g were injected ip with 10 mg/kg of diethylnitrosamine (DEN) 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after Ph, groups of 6 rats were fed a control diet or diets containing Pb, FM BP-6, or HBB. Rats not partially hepatectomized or given DEN were fed Pb, FM BP-6 or HBB at the same levels. At 6 months rats were killed and tissue samples were collected for histologic and histochemical studies. Enzyme altered foci were identified by using gamma-glutamyl transpeptidase. FM BP-6 caused decreased weight gain, thymic atrophy and enlarged and vacuolated hepatocytes. (no Refs)

22. THE EFFECT OF ANALGESICS ON MORRIS HEPATOMA GROWTH, SERUM PROTEIN, ALBUMIN AND GLOBULIN OF RATS FED 25% CASEIN DIETS (MEETING ABSTRACT).

Knight EM, Deedua I, Fakunle JB, Nzelibe G, Criss W
Department of Nutrition, Howard University, Washington, DC
Med Pediatr Oncol; 10(1):100 1982

The effect of salicylic acid (aspirin) and salicylamide (SAM) on growth of Morris Hepatoma was studied in rats. Serum protein, albumin and globulin were analyzed to determine the effect of tumor incidence and drug treatment on protein nutritional status of the animals. Male buffalo rats were maintained on 25% casein diets for 2 weeks, and then fed experimental diets of 25% casein supplemented with 0.3% aspirin or 1% SAM, three days prior to the injection of Morris Hepatoma 7800 (1x10(6) cells). The animals were kept on the diets for 4 weeks after tumor transplant and then sacrificed. Tumors and livers were excised and weighed, and serum stored for protein and albumin analysis. Serum protein in tumor bearing animals, drug treated and non-drug treated, was not significantly different. Significantly lower serum globulin and higher albumin to globulin ratio (A/G ratio), were found in the SAM treated animals. The latency period for tumors in the aspirin treated animals was significantly longer than in SAM or non-drug treated animals (33% and 67% of the animals had palpable tumors 11 and 12 days respectively after tumor injection; versus 90-100% of the animals in the SAM or 25% casein groups). Tumor areas (length x width; sqcm) were significantly lower in the group of animals fed aspirin. These results show that aspirin supplemented casein diet inhibits the growth of Morris Hepatoma 7800 while the effects due to SAM treatment were insignificant. The possible mechanism for tumor growth reduction in aspirin treated animals, may be due to the direct inhibitory effect of prostaglandin synthesis by aspirin, since there is a direct relationship between prostaglandin concentration and tumor growth. There was a negative correlation between tumor area, albumin and A/G ratio, which suggests decreased formation of albumin in the liver or increased urinary losses. Protein, albumin, globulin and A/G ratio were not below the normal values for the rat in this study; therefore, drug treatment and tumor incidence did not alter the protein nutritional status of the animals. (no Refs)

23. SURGICAL AND DIETARY INJURY AND LIVER TUMORS IN B6C3F1 MALE MICE (MEETING ABSTRACT).

Newberne PM, Clark AJ, DeCamargo J
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

Male weanling B6C3F1 strain mice were fed a controlled semisynthetic diet with or without choline. Some mice from each group were subjected to partial hepatectomy but no other treatment. Groups of animals were sacrificed at 3, 6, 9, or 12 months. At the three months sacrifice all of the animals fed the choline-deficient diet had liver changes suggestive of nodule formation whereas the supplemented animals had none. At 6 months, all choline deficient animals and about half of those that received partial hepatectomy had grossly visible nodules up to 1 cm in diameter protruding from the surface of the liver. Microscopic examination indicated that while fatty liver and fibrosis were components of the choline-deficient diet there were numerous nodules that had excluded fat and were labeled heavily with tritiated thymidine. Partial hepatectomy of choline-deficient rats appeared to protect against nodule formation to some degree with the incidence in this group midway between choline deficiency and those that were fed the normal supplemented diet. DNA synthesis and liver cell proliferation were enhanced in animals fed either the deficient diet or the deficient diet plus partial hepatectomy or the control diet plus partial hepatectomy. Histochemical, biochemical, and morphologic assessment of sequential studies at shorter intervals during the development of tumors have indicated that the liver of the B6C3F1 mouse is 'initiated' at least by the time they are weaned and that non-specific factors can enhance the formation of tumors in the liver that is already predisposed to neoplastic change. (no Refs)

24. HEPATOTOXICITY OF DEOXYCHOLIC ACID IN MICE AND RATS WITH SPECIAL REFERENCE TO GERM-FREE CONDITIONS.

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Nara Igaku Zasshi; 33(1):71-97 1982

Deoxycholic acid (DOC) was administered by gastric intubation or iv infusion to 4-wk-old ICR mice, 4-wk-old SLC/Wistar rats, Fischer 344 rats, and germ-free (GF) Fischer rats, and the toxicity and carcinogenicity of the DOC was studied. The LD50 of DOC administered by intubation was 1,200 mg/kg in male ICR rats and 1,000 mg/kg in females. The LD50 in male Wistar and Fischer rats were 1,150 mg/kg and 1,000 mg/kg, respectively, and in the corresponding females, 1,480 mg/kg and 1,660 mg/kg, respectively. Results of subacute toxicity studies using 500, 500, or 700 mg/kg of DOC (intubation, every day for 2-3 wk) indicated that the rats were more susceptible than the mice to DOC toxicity and the males more than the females. Proliferation of intrahepatic bile ducts was prominent in some Wistar rats fed 0.6% DOC pellets for 80 wk, but there was no malignancy of hepatocytes or of bile ducts. Results of studies of conjugated bile acids and free bile acids in the rats given DOC, together with the results of the other experiments, suggested that DOC does not initiate, but rather that it promotes, hepatic or intestinal carcinogenesis. (68 Refs)

25. DIETARY OROTIC ACID, A NEW SELECTIVE GROWTH STIMULUS FOR CARCINOGEN ALTERED HEPATOCYTES IN RAT.

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Cancer Lett; 16(2):191-196 1982

A new dietary protocol is described wherein feeding a diet containing orotic acid (OA), a precursor of pyrimidine nucleotide biosynthesis, selectively stimulates the growth of 1,2-dimethylhydrazine (DMH) modified cells to form gamma-glutamyltransferase positive hepatocytes in Fisher F344 rats. Experimental protocol is presented in detail. Following the 'initiating' treatment with DMH, six foci/square cm (cm2) were obtained in the liver of rats fed 1% OA diet compared to one or two foci/cm2 observed in the liver of rats fed a control diet. Prolonging the OA diet to 10 wk resulted in an increase in the number of foci up to 14/cm2. When feeding OA was coupled with administration of a single necrogenic dose of CCl4, the number of foci generated increased from 6-24 in 5 wk, and from 14-39 in 10 wk. Administration of CCl4 even in the absence of OA resulted in an increase in the number of foci. Results suggested that not only the carcinogen-altered hepatocytes differ from the normal in the response to an exogenous liver cell proliferation stimulus, but also that OA further modifies the carcinogen-altered cells in such a way that they respond to an even greater extent to the liver cell proliferative stimulus. (19 Refs)

26. IMMUNE REACTIONS IN INADEQUATE NUTRITION AND IN AFLATOXIN CARCINOGENESIS.

Popov AA, Krystev LP, Kamenova BB
Inst. Gastroenterology and Nutrition, Sofia, Bulgaria
Vopr Pitan; (3):58-60 1982

Relationships between inadequate nutrition, humoral immunity, and incidence of aflatoxin-induced tumors were studied in male Wistar rats. The aflatoxin was administered ip, 10 ug/rat, 5x/wk. Rats in Group 1 received standard nutrition, while rats in Group 2 received a reduced ration. Colonic leiomyosarcomas, but no hepatomas, were observed to develop. The incidence of the sarcomas in the Group 2 rats was significantly lower than that in the Group 1 rats. The reduced incidence of aflatoxin-induced tumors in the Group 2 rats was shown to be associated with immunological deficiency. It was assumed that the immune deficiency was accompanied by inhibition of enhancement in the course of aflatoxin carcinogenesis. (14 Refs) (In RUS)

27. PROLIFERATIVE LIVER LESIONS AND SEX STEROIDS IN RATS (MEETING ABSTRACT).

Schuppler J, Schulte-Herman R, Gunzel P
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The steroids which increase the incidence of proliferative liver lesions (PLL) have not been shown to have the characteristics usually associated with classical hepatocarcinogens such as diethylnitrosamine. Therefore, another mechanism must be assumed. A possible explanation is given by the ability demonstrated for a few steroids to promote preneoplastic islands induced by diethylnitrosamine, resulting in an increase in tumor incidence over rats given only the carcinogen. Spontaneous preneoplastic islands in rats occur in various incidences in different strains and we have recently shown that their reaction to steroids enhanced proliferation is the same as the effect on preneoplastic islands produced by classic carcinogens. Sex steroids also enhance the growth of normal hepatocytes. It, therefore, seems reasonable to assume that sex steroids produce PLLs by acting on spontaneous preneoplastic lesions and not by the mechanisms usually associated with classic carcinogens. Extrapolating the incidence of PLLs in rats to a risk in humans may be highly misleading because of different pharmacokinetic patterns. Even in rats treated orally for two years with sex steroids dosed as multiples of the human contraceptive dose, resorption and bioavailability may vary by a factor of 10 or more. It is therefore inappropriate to state that one sex steroid is more active in the production of PLLs than another, unless the data from pharmacokinetic studies are taken into account. In summary, available evidence shows that sex steroids act as tumor promotors and enhance the growth of normal hepatocytes. It is extremely doubtful whether a sex steroid producing PLLs in the rat after two years of oral treatment can be classified as an initiating tumorigen for the rat and, because of the high incidence of spontaneous preneoplastic lesions in rats, whether any substantial risk for humans can be inferred. (no Refs)

28. SIALIC ACID METABOLISM IN NUTRITIONALLY-MODULATED HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Fox OF, Kishore GS, Graham SA, Carubelli R
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Fed Proc; 41(3):337 1982

The sialic acid content and the activities of the enzymes responsible for the activation, transfer and hydrolysis of sialic acid were investigated in the livers of male Sprague-Dawley rats treated with 2-acetylaminofluorene (AAF). Basal diets containing 20% corn oil, 18% coconut oil + 2% linoleic acid or 2% linoleic acid, with or without supplementation with 0.7% (w/w) butylated hydroxytoluene (BHT) were used. The carcinogenic diets contained 0.05% (w/w) AAF. AAF-treated rats and age-matched controls fed basal diets, were killed after 14-17 weeks of treatment. The livers were used for histological, chemical and enzymological studies. Rats fed high-fat diets showed earlier and higher incidence of AAF-induced hyperplastic nodules (HPN); BHT supplementation greatly retarded the development of these lesions. Increases in sialic acid content and in the levels of CMP (cytosine monophosphate)-sialic acid synthetase and neuraminidase, both cytosolic and particulate, were observed in the livers from AAF-treated rats. Sialyltransferase activity, on the other hand, was not affected. BHT supplementation resulted in lower levels of sialic acid and CMP-NANA synthetase in rats fed low fat and saturated-fat diets; proportional reductions were observed in AAF-treated and in control rats. The chemical and enzymatic changes observed in AAF-treated rats are consistent with an increased turnover of sialoglycoconjugates during the carcinogenic process. (no Refs)

ACTIVATION AND METABOLISM OF HEPATOCARCINOGENS

29. DRUG METABOLIZING ENZYMES IN THE LIVERS AND HEPATIC TUMORS OF RATS TREATED WITH POLYCHLORINATED BIPHENYLS (MEETING ABSTRACT).

Reddy G, Cihla HP, Weltman RH, Norback DH
William S. Middleton Memorial Veterans Administration Hospital,, University of Wisconsin Madison, WI, 53705
Toxicologist; 2(1):64 1982

Hepatic drug metabolizing enzyme activities in the livers of rats were investigated after chronic exposure to Aroclor 1260 (PCB) or 2,3,6,2',3',6'-hexachlorobiphenyl (HCB). Sprague-Dawley rats of both sexes were fed diets containing PCB (100 ppm for 16 mo followed by 50 ppm) or HCB (100 ppm for 9 mo followed by 5 mo period of intermittent exposure followed by 100 ppm). After 24 mo they were fed a normal diet until sacrifice. The hepatic microsomal enzyme activities of aldrin epoxidase (AE), styrene oxide epoxide hydrolase (EH), and cytosolic glutathione S-epoxide transferase (GT) and the quantity of cytochrome P-450 were measured. Livers from male rats fed HCB contained enzyme levels equal to or decreased from that of controls. Livers from PCB fed male rats showed enzyme levels 1.3 to 4 fold higher than that of controls. Livers from female rats exposed to HCB showed enzyme levels equal to or decreased from control levels. Liver tumors or surrounding tissues of female rats fed PCB showed 2 to 10 fold higher enzyme activities and cytochrome P-450 content than controls. AE activity was slightly higher in surrounding tissues than in tumor, while EH activity was 1.5 times higher in the tumors than in the surrounding tissues. The levels of P-450 and GT in tumors and in surrounding tissue were nearly equal. In conclusion, increased enzyme activities and P-450 content persisted 2 to 5 months after discontinuation of PCB exposure. (no Refs)

30. INHIBITION OF DIMETHYLNITROSAMINE METABOLISM BY SOME HETEROCYCLIC COMPOUNDS AND BY SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE IN THE RAT.

Phillips JC, Bex C, Lake BG, Cottrell RC, Gangolli SD
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Cancer Res; 42(9):3761-3765 1982

Pretreatment of rats with a number of nitrogen-containing heterocyclic compounds was found to inhibit markedly the metabolism of dimethylnitrosamine (DMN) in terms of both CO2 excretion and decline in blood DMN concentration. However, many of these compounds had either much less or no inhibitory effect on the in vivo metabolism to CO2 of a typical mixed-function oxidase substrate, aminopyrine. In addition, a number of model inhibitors of monoamine oxidase (MAO) activity also inhibited DMN metabolism in the intact animal, and a number of primary amines, known substrates of hepatic MAO, inhibited DMN metabolism but not that of aminopyrine in the isolated perfused liver system. These results, together in vitro data and previously reported studies on the effect of MAO inhibitors and substrates on the mutagenicity of DMN, suggest that the metabolism and bioactivation of DMN may be in part mediated by a MAO type of enzyme activity. (Author abstract) (46 Refs)

31. CHARACTERIZATION AND PROPERTIES OF THE DNA ADDUCTS FORMED BY THE HEPATOCARCINOGEN N-METHYL-4-AMINOAZOBENZENE IN TARGET AND NON-TARGET ORGANS.

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Diss Abstr Int [B]; 42(10):4005-B 1982

The carcinogenic aminoazo dyes, typified by N-methyl-4-aminoazobenzene (MAB), are believed to be metabolized to electrophilic N-sulfonyloxy esters which bind covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. Since the persistence of DNA-carcinogen adducts has been demonstrated to correlate with the susceptibility of specific tissues to tumor formation, the identity and persistence of the DNA adducts formed by MAB in target (liver) and non-target (kidney and spleen) organs has been determined. In order to produce quantities of adducts sufficient for structural determination, the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene (N-BzO-MAB) was reacted in vitro with calf thymus DNA. After enzymatic hydrolysis of the DNA, six MAB-DNA adducts were detected by high pressure liquid chromatographic analysis. In vivo adducts corresponding to all six of the in vitro products were detected after one to five weeks of feeding diets containing 0.06% (3H)MAB. Comparison of the adducts isolated from target and non-target tissues revealed a number of differences during the treatment period; however, the only persistent alteration was the increased levels of 3-(deoxyguanosin-N2-yl)-MAB (N2-dG) in hepatic DNA. N2-dG, therefore, is the adduct most likely to be responsible for the induction of hepatic tumors by MAB. (no Refs)

32. STUDIES ON THE FORMATION OF AN AFLATOXIN B1-8,9-OXIDE CONJUGATE WITH GLUTATHIONE (AFB1-GSH) IN VITRO AND IN VIVO (MEETING ABSTRACT).

Garner RC, Hertzog PJ, Lindsay-Smith JR
Cancer Research Unit University of York, Heslington, York, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Incubation of aflatoxin B1 (AFB1) and [14C]-labelled glutathione with either a rat or mouse liver post-mitochondrial, supernatant (PMS) and subsequent reversed-phase high pressure liquid chromatography of the metabolites revealed the formation of a AFB1-GSH conjugate. This metabolite eluted prior to other AFB1 metabolites such as AFM1 and AFP1. Mouse PMS produced more of this metabolite than rat PMS. UV spectra of AFB1-GSH indicated that linkage of GSH to AFB1 was through a sulphur rather than a nitrogen group. Acid hydrolysis (IN HCl at 100 degrees for 60 mins) of AFB1-GSH released the glutamic residue to leave a AFB1 conjugate that was not AFB1-8, 9-diol. A metabolite with an identical retention time on reversed-phase chromatography to AFB1-GSH was also found in the bile of cannulated rats administered AFB1. Despite the formation of this GSH conjugate in vitro and in vivo, addition of GSH to the top-agar of a Salmonella/microsome assay of AFB1 does not inhibit mutagenicity. (no Refs)

33. INHIBITION OF AFLATOXIN B1 CARCINOGENESIS IN RAINBOW TROUT BY DIETARY BETA-NAPHTHOFLAVONE (BETA-NF), AND INDOLE-3-CARBINOL (I-3-C) (MEETING ABSTRACT).

Hendricks JD, Nixon JE, Bailey GS, Sinnhuber RO
Department of Food Science and Technology, Oregon State University, Corvallis, OR, 97331
Toxicologist; 2(1):102 1982

Several compounds such as flavonoids, selenium, antioxidants and certain vitamins reportedly reduce the induction of cancer in experimental animals, and many function by affecting the mixed-function oxidase (MFO) system. The following compounds: 50 and 500 ppm beta-NF, 1000 ppm flavone, 1000 ppm of a tangeretin-nobilitin mixture, 1000 ppm beta-ionone, 1000 ppm I-3-C and 2000 ppm quercetin were examined for protection against aflatoxin B1 (AFB1) hepatocarcinogenesis and induction of the MFO system in rainbow trout. These compounds were fed to fingerling rainbow trout for 2 months. At that time the activity of several MFO enzymes and cytochrome P450 content were measured and the trout were exposed to 20 ppb AFB1 for 10 days in the same diets. After feeding the test diets without AFB1 for another month and basal diet for 11 months, the tumor incidence was determined. Beta-NF induced the trout MFO system in a dose-dependent manner while tangeretin-nobilitin was less effective. Flavone, quercetin, beta-ionone and I-3-C did not induce the MFO system. I-3-C and beta-NF provided marked protection against AFB1-induced hepatocarcinogenesis, while the other compounds were ineffective. Tumor incidences were 5.1% for 1000 ppm I-3-C, 7.5% for 500 ppm beta-NF and 19.6% for 50 ppm beta-NF, compared to 44.9% for the AFB1-positive control. (no Refs)

34. EFFECT OF INCREASING LEVELS OF DIETARY PROTEIN ON THE METABOLIC ACTIVATION AND COVALENT BINDING OF AFLATOXIN B1 (MEETING ABSTRACT).

Hayes JR, McCall CO, Bagley DM
Department of Pharmacology Medical College of Virginia, Virginia Commonwealth University, Richmond, VA
Toxicologist; 2(1):25 1982

Low dietary protein levels (5%) decrease the hepatocarcinogenicity of aflatoxin B1 (AFB1), in part due to decrease in hepatic microsomal mixed function oxidase (MFO) activity, which activates AFB1 to its ultimate carcinogen. Although low levels of dietary protein are consumed by certain populations, others may consume protein above that required for maintenance. This study was designed to ascertain the effects of increasing levels of dietary protein on the metabolic activation of AFB1. Male, weanling Sprague-Dawley derived rats fed the AIN-76 semi-purified diet with casein levels of 5, 10, 20, 30 and 40% for 10 days. Body weight increased until protein levels reached 20% and then became asymptotic. Liver weights were higher only in the 5 and 10% groups due to lipid infiltration. Microsomal protein increased with dietary protein up to 20% and then became asymptotic. N-demethylation of ethyl-morphine (EM) increased until dietary protein levels reached 30% and then became constant. Cytochrome c reductase activity and cytochrome P-450 levels followed a trend identical to EM metabolism. In vitro metabolic activation of AFB1 to a produce(s) capable of covalently binding DNA increased until a level of 30% protein was reached and then became asymptotic. In vivo covalent binding of an AFB1 metabolite(s) to hepatic DNA, RNA and protein followed the same trend as the in vitro studies. Inappropriately low levels of dietary protein may be protective in respect to AFB1 carcinogenicity, but high levels may increase risk. (no Refs)

35. METABOLISM OF AFLATOXIN B1 (AFB1), AFLATOXIN G1 (AFG1) AND VITAMIN C INTAKE BY GUINEA PIG LIVER PREPARATION IN VITRO.

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Biochem Pharmacol; 31(14):2327-2330 1982

Male and female guinea pigs weighing 150-200 g were divided into three groups, with equal number of males and females in each group. They were fed an experimental diet which varied as follows: Group I, 0 mg vitamin C/g of diet; Group II, 1.08 mg/g and Group III, 5.4 mg/g, for 28 days. Twenty-four hr after the last feeding, liver slices and 9,000 g supernatant were prepared from each group, according to sex, and used for enzyme assays. For the demethylation assay, enzyme activity expressed as amount of formaldehyde produced from AFB1 or AFG1/hr/g fresh liver was seen to increase with the two levels of ascorbic acid intake in females. Males showed an enhancement of activity only in Group II and remained with the same production of formaldehyde as above in Group III. Although in each dietary group, the activity was higher in males than in females the variation in the amount of formaldehyde produced from one group to another was higher with females than with male guinea pigs. However with both sexes, the production of formaldehyde from AFG1 was greater than from AFB1. For the hydroxylation assay, enzyme activity was expressed as amount of metabolites (a) and (b) produced. Compared to Group II, which offered a control level of ascorbic acid, Group I fed without vitamin C showed a decreased production of metabolite (a) with males and females. Moreover, high intake of ascorbic acid in Group III decreased the production of metabolite (a) and (b) in males, while in female guinea pigs the reduction was observed only with (b). (Author abstract) (25 Refs)

36. THE RELATIONSHIP BETWEEN AGING AND CANCER: AGE-RELATED CHANGES IN THE ABILITY OF THE LIVER TO METABOLIZE AFLATOXIN B1 (MEETING ABSTRACT).

Richardson A
Department of Chemistry, Illinois State University, Normal, IL, 61761
16th Annual Meeting of the Great Lakes ACS Region, June 7-9, 1982, Normal, Illinois. American Chemical Society 101 pp., 1982.

Although the incidence of cancer increased dramatically with increasing age, the exact relationship between aging and cancer is not clearly understood. It is possible that changes in biochemical reactions, which arise from the aging process, may play a role in the development of cancer induced by chemical carcinogens. However, results from research in the area of aging and cancer are contradictory. Previous investigators have used a holistic approach to studying the relationship between aging and cancer. Therefore, we focused on the effect of aging on the metabolism of the chemical-procarcinogen, aflatoxin B1 (AFB1) by liver extracts (S-9 and microsomes) from 4-to 27-month old male Fischer F344 rats. The Ames Salmonella Bioassay was used to quantify the activation of AFB1. The number of revertants produced by the S-9 or microsomes decreased 40 to 50% between 12 and 27 months of age. The formation of AFB1-DNA adducts by the S-9 fraction also decreased with increasing age. The metabolism of AFB1 to chloroform-soluble, water-soluble, and alcohol-insoluble metabolites also decreased as a function of age. Except for aflatoxicol, the formation of all chloroform-soluble metabolites of AFB1 decreased between 12 and 27 months of age. However, the formation of aflatoxicol increased slightly with age. The age-related decrease in AFB1 metabolism was correlated to a decrease in the mixed function monooxygenase system and could potentially result in an increase in the vulnerability of an organism to the carcinogenic effects of AFB1. (no Refs)

37. EFFECT OF AGE ON THE ABILITY OF RAT LIVER TO METABOLIZE THE CHEMICAL CARCINOGEN AFLATOXIN B1.

Jayaraj AA
Illinois State University, Normal, IL
Diss Abstr Int [B]; 42(10):4046-B 1982

The ability of liver fractions from 4-to 30-month-old Fischer F344 rats to activate and metabolize aflatoxin B1 (AFB1) in vitro was studied. The activation of AFB1 was measured by the Salmonella/microsome test and by its ability to bind to DNA in vitro. The metabolism of AFB1 was determined by measuring the conversion of AFB1 to water-soluble and CHCl(3)-soluble metabolites. The activation of AFB1 to compounds that are mutagenic in the Samonella/microsome test and to compounds that bind to DNA in vitro by liver S-9 and microsomes from male Fischer F344 rats decreased approximately 50% with increasing age. The in vitro metabolism of AFB1 by liver S-9 and microsomal fractions decreased significantly with increasing age. The metabolism of AFB1 to water-soluble and CHCl(3)-soluble metabolites was lower for liver preparations from 26-month-old than for 4 and 12-month-old male rats. The proportion of aflatoxicol produced by liver S-9 from male Fischer F344 rats increased approximately two-fold between 4 and 26 months of age. This increase could potentially increase the sensitivity of the organism to AFB1-induced hepatocarcinogenesis. Liver microsomal cytochrome P450 decreased approximately 50% between 4 and 26 months of age. A 60% decrease in the benzopyrene hydroxylase and benzphetamine demethylase activities was observed between 4 and 26 months of age. No age-related change in the ability of S-9 fractions from the liver of female Fischer F344 rats to activate AFB1, to its metabolites that are mutagenic in the Salmonella/microsome test was observed. (no Refs)

38. RAPID DECREASES IN N-HYDROXY-2-ACETYLAMINOFLUORENE SULFOTRANSFERASE ACTIVITY OF LIVER CYTOSOLES FROM RATS FED CARCINOGEN (MEETING ABSTRACT).

Ringer DP, Kampschmidt K, King RL, Jackson S, Kizer DE
The Noble Foundation Inc., Ardmore, OK, 73401
Fed Proc; 41(3):927 1982

Sulfation of N-hydroxy-2-acetylaminofluorene (N-OH-AAF) yields a candidate ultimate carcinogen for hepatocarcinogenesis in rats. Employing an assay for N-OH-AAF sulfotransferase described by Mulder et al, we monitored this activating pathway during the initial phase of hepatocarcinogenesis produced by feeding rats a diet of 0.05% AAF. Our studies revealed an immediate and precipitous decrease (4-5-fold) in N-OH-AAF sulfotransferase activity following 1 to 5 days of feeding, and activity remained at low levels with continuous feeding of AAF diet throughout 4 weeks. Other known carcinogens, eg, aflatoxin, diethylnitrosamine and thioacetamide, caused equally significant drops in N-OH-AAF sulfotransferase activity by 7 days of feeding, while non-carcinogenic compounds, eg, p-aminoazobenzene, fluorene and sodium barbital, failed to reduce N-OH-AAF sulfotransferase activity. Parallel monitoring of rat serum GOT (glutamic oxalic-acetic) activity during AAF-induced decreased sulfotransferase activity failed to indicate appreciable hepatocellular toxicity. Perhaps N-OH-AAF sulfotransferase activity can be used as an early indicator of hepatocarcinogenesis. (no Refs)

39. 2-ACETYLAMINOFLUORENE (AAF) DEPENDENT INCREASES IN EPOXIDE HYDROLASE: SPECIES, STRAIN AND SEX DIFFERENCES (MEETING ABSTRACT).

Gralchen ME, Dent JG
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):101 1982

Exposure of rats to hepatocarcinogens causes substantial increases in hepatic microsomal expoxide hydrolase (EH) activity. The potency of compounds in increasing EH is related to their carcinogenic potency. The objective of this study was to investigate the relationship between hepatocarcinogenicity and increases in epoxide hydrolase using the known species, strain and sex differences in susceptibility to AAF carcinogenicity. Following administration of AAF in the diet or via ip injections, liver microsomes or 10,000 g supernatant was prepared. EH activity was measured with benzo(a)pyrene-4,5-oxide as substrate. Three daily ip injections of AAF, at doses between 5 and 80 mg/kg/day, caused dose-related increases in EH in male F-344 and CD rats. The log-linear dose response obtained has the same slope in both strains and the ED50 was 13 mg/kg/day. The maximum increase observed was 350% of control activity in both strains. No increase in EH activity was detected in guinea pigs treated with AAF at doses between 40 and 240 mg/kg/day for 3 days. In DBA2 and C57Bl6 mice fed 0.02% AAF for 2 weeks, decreases in EH were observed. By comparison, F-344 male rats fed this diet exhibited a 460% increase in EH activity. Female rats, mice and guinea pigs are poor N-hydroxylators of AAF and are resistant to the carcinogenic action of AAF. (no Refs)

40. BINDING OF BENZO(A)PYRENE TO HEPATIC CYTOSOLIC PROTEIN ENHANCES ITS MICROSOMAL OXIDATION.

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Biochem Biophys Res Commun; 104(3):1093-1101 1982

A study with 14C-benzo(a)pyrene (BP) indicates that its binding to a protein in rat liver cytosol facilitates its oxidation by microsomal enzymes. Cytosols (100,000 x gravity supernatants) were prepared from the liver of Sprague-Dawley rats. The cytosols saturated with BP were subjected to Sephadex G-100 gel permeation chromatography. Analysis of the fractions resulted in two peaks of protein bound radioactivity. Glutathione-S-transferase activity (towards 1-chlor 2,4-dinitrobenzene as substrate) eluted as a single major peak which coincided with one peak of protein bound BP. Oxidation of cytosolic protein bound BP (GST rich fractions) by microsomes from control or 3-methylcholanthrene-treated rats was significantly enhanced as compared to ethanol suspended BP. Production of oxidized products from the protein-bound BP was dependent on incubation time and microsomal protein concentration, it required NADPH and was inhibited by monooxygenase inhibitors (alpha-naphthoflavone, 1-benzylimidazole, metyrapone, and SKF 525A). Coemergence of BP binding-protein with GST suggests that the soluble protein could be one of the glutathione-S-transferases. (15 Refs)

41. BENZO[A]PYRENE METABOLITES: FORMATION IN RAT LIVER CELL-CULTURE LINES, BINDING TO MACROMOLECULES, AND MUTAGENESIS IN V79 HAMSTER CELLS.

Selkirk JK, MacLeod MC, Kuroki T, Drevon C, Piccoli C, Montesano R
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 3(6):635-639 1982

Benzo[a]pyrene was metabolized in liver cell lines derived from BD-IV and BD-VI rats which included several chemically-transformed lines (IAR-6-1; IAR-19; IAR-28), one spontaneous transformant (IAR-27) as well as one nonmalignant line (IAR-20). Cultures were treated with tritiated benzo[a]pyrene over a 5-day period. The cells and medium were extracted with ethyl acetate and the distribution between organic-soluble and water-soluble metabolites determined. Organic-soluble metabolites consisting of dihydrodiols, phenols and quinones were determined by high-pressure liquid chromatography, and macromolecular binding of BP to each cell line was measured over a 24-hr period. Comparisons between binding and overall metabolism were not directly proportional in these liver cell lines. However, there was a positive correlation for benzo[a]pyrene mutagenesis in the V-79 hamster cell assay with 8-azaguanine as a marker when the cell lines with the highest (IAR-20) and lowest (IAR-27) metabolic competence were used as activating cell layers. (Author abstract) (28 Refs)

42. FORMATION OF MUTAGENIC METABOLITES FROM BENZO(ALPHA)PYRENE AND 2-AMINOANTHRACENE BY THE S-9 FRACTION FROM THE LIVER OF THE NORTHERN PIKE (ESOX LUCIUS): INDUCIBILITY WITH 3-METHYLCHOLANTHRENE AND CORRELATION WITH BENZO[ALPHA]PYRENE MONOOXYGENASE ACTIVITY.

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Chem Biol Interact; 41(1):1-13 1982

The mutagenicity of benzo[a]pyrene and 2-aminoanthracene in the Ames test using the S-9 fraction from the liver of the Northern pike (Esox lucius) was tested. S-9 fractions were prepared both from fish injected intraperitoneally with 3-methylcholanthrene and from control animals. In addition benzo[a]pyrene monooxygenase activity was assayed in the same S-9 fractions used in the Ames test. S-9 fractions from the liver of the Northern pike were found to convert benzo[a]pyrene and 2-aminoanthracene to mutagenic metabolites. The number of revertants obtained was increased 2-4-fold in the case of 2-aminoanthracene and 3-14-fold in the case of benzo[a]pyrene by pretreatment of the pike with a single intraperitoneal injection of 3-methylcholanthrene. This injection also caused a two- to six-fold increase in the benzo[a]pyrene monooxygenase activity of the S-9 fractions used. These increases in mutagenicity and activity occur mainly during the first 4-12 days after the injection, but further small increases are observed for as long as 60 days. A strong positive correlation was found between the benzo[a]pyrene monooxygenase activity of the S-9 fractions used and their ability to give rise to revertants in the Ames test using 2-aminoanthracene or benzo[a]pyrene. This indicates that the major determining factor in the production of reactive metabolites which attack DNA in this in vitro system is the activity of the Phase I cytochrome P-450 system. (Author abstract) (26 Refs)

43. METABOLISM OF (+-)-TRANS-7,8-DIHYDROXY-7,8-DIHYDRO-BENZO[A]PYRENE IN MOUSE LIVER MICROSOMES AND THE EFFECT OF 2(3)-TERT-BUTYL-4-HYDROXYANISOLE.

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Carcinogenesis; 3(6):697-701 1982

The metabolism of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (BP-7,8-diol) was examined using liver microsomes from mice maintained either on a standard laboratory food diet or on a mixture of ground food pellets and 2(3)-tert-butyl-4-hydroxyanisole (BHA, 7.5 g/kg food). Dietary BHA had a statistically significant inhibitory effect both on the formation of polar metabolites of BP-7,8-diol and on the covalent binding of reactive products to calf thymus DNA. When BHA (20 uM) was added in vitro to the microsomal incubation system, both the metabolism of BP-7,8-diol and the covalent binding of BP-7,8-diol metabolites to DNA, was reduced by approx 50% using either type of microsomes. The binding of [14C] 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene to calf thymus DNA was not affected by the presence of BHA. the reduced metabolism of BP-7,8-diol in microsomes from BHA-treated mice compared to control was not due to the effect of residual BHA in the microsomal preparation. These results show that BHA acts as a potent inhibitor of the activation of the proximate carcinogen BP-7,8-

diol to reactive, DNA-binding products both when administered as a dietary constituent and as an additive to microsomal incubation systems. Both of these properties may be of relevance to the inhibitory effect of BHA on benzo[a]pyrene carcinogenesis. (Author abstract) (56 Refs)

44. EFFECT OF 2(3)-TERT-BUTYL-4-HYDROXYANISOLE ON BENZO[A]PYRENE METABOLISM AND DNA-BINDING OF BENZO[A]PYRENE METABOLITES IN ISOLATED MOUSE HEPATOCYTES.

Dock L, Cha YN, Jernstrom B, Moldeus P
Dept. Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm, Sweden

Chem Biol Interact; 41(1):25-37 1982

Benzo[a]pyrene (BP) metabolism and the conjugation and DNA-binding of BP metabolites, was studied using isolated hepatocytes from mice maintained on a diet containing 2(3)-tert-butyl-4-hydroxyanisole (BHA) (7.5 g/kg food) to discover the mechanisms involved in the anticarcinogenic effects of this antioxidant. The antioxidant feeding produced: (a) profound differences in the BP metabolite pattern, (b) no increase in the levels of either the glucuronic acid, the sulfate or the glutathione conjugates and (c) a marked decrease in the level of BP metabolites bound to intracellular DNA. Therefore, the inhibition of DNA-binding observed after administration of BHA, may be due to the change in BP metabolism rather than to an increase in the conjugation of reactive metabolites. (Author abstract) (39 Refs)

45. DIFFERENTIAL EFFECTS OF DIETARY AND INTRAPERITONEAL ADMINISTRATION OF ANTIOXIDANTS ON THE ACTIVITIES OF SEVERAL HEPATIC ENZYMES OF MICE.

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Drug Metab Dispos; 10(4):434-435 1982

Biochemical effects of ip administration 2(3)-tert-butyl-4-hydroxyanisole (BHA), 1,2-dihydro-6-ethyl-2,2,4-trimethylquinoline (EQ), and disulfiram (DSF) on female CD-1 mice were compared with those previously observed by dietary administration of the antioxidants. Dietary administration of BHA and EQ produced marked enlargement of the liver. In contrast, ip administration of the antioxidants for the same duration did not alter the liver weights. Pretreatment of mice with DSF, either in the diet or by ip injections, did not produce any changes in their liver weights. Feeding of BHA, EQ, and DSF all produced disproportionate increases in the activity of both flavin reductases. BHA produced a moderate increase of NADPH-cytochrome c reductase activity without any changes in cytochrome P450 levels. No effects on aminopyrine N-demethylation were noted but a marked increase of p-hydroxylation of aniline and a significant decrease of benzopyrene mono-oxidation occurred. Dietary EQ produced an increase in NADPH-cytochrome c reductase activity and marked elevation of cytochrome P450 levels. Concurrent with the increases, the rates of N-demethylation and of hydroxylation were greatly increased. However, the oxidation rate of benzopyrene was reduced. Changes produced by DSF were small if any. Differential effects produced on glucose 6-phosphate, glutathione reductase, and uridine diphosphate-glucose dehydrogenase are described. (17 Refs)

46. CARCINOGENESIS BY HYDROXYALKYL NITROSO COMPOUNDS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:205 1982

It is known that Nitrosodiethanolamine and nitrosobis-(2-hydroxypropyl)amine are weaker carcinogens than their parents, nitrosodiethylamine and nitrosodi-n-propylamine. Through metabolic activation they would be expected to give rise to the alkylating moieties hydroxyethyl- and 2-hydroxypropyl-, respectively, which could relate to their carcinogenic action in the liver and esophagus of the rat. The directly acting nitrosohydroxyethylurea and nitrosooxazolidone give rise to a hydroxyethylating agent without metabolic activation. Similarly, nitroso-2-hydroxypropylurea and nitroso-5-methyloxazolidone give rise to a 2-hydroxypropylating agent without activation. All four nitrosamides are skin carcinogens of comparable potency, when applied topically in acetone solution to the skin of female Swiss mice for 45 weeks at equimolar concentration. In contrast, when given intragastrically to rats by gavage, there are large differences in carcinogenic activity. Both nitrosooxazolidone and its 5-methyl derivative induce mainly forestomach carcinomas. Nitroso-2-hydroxypropylurea induced thymic leukemias and lymphomas. Nitrosohydroxyethylurea induced tumors at many sites, including osteogenic sarcomas, colon adenocarcinomas, stomach adenocarcinomas and lung carcinomas. This suggests that factors other than just the formation of an alkylating agent have an important bearing on organ specific tumorigenesis by N-nitroso compounds. (no Refs)

47. DOSE DEPENDENT INDUCTION OF RAT LIVER MICROSOMAL CYTOCHROME P-450 AND MICROSOMAL ENZYMATIC ACTIVITIES AFTER INHALATION OF TOLUENE AND DICHLOROMETHANE.

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Acta Pharmacol Toxicol (Copenh); 51(2):108-114 1982

Sprague-Dawley rats were exposed, by inhalation, to toluene and dichloromethane (500, 1,500 or 3,000 ppm) and to benzene (1,500 ppm) for 3 days. Toluene and benzene increased the concentration of liver microsomal cytochrome P-450. A dose dependent increase in the in vitro liver microsomal formation of several metabolites of biphenyl and benzo(a)pyrene was observed for both dichloromethane and toluene. At the highest dose-level the increase in the in vitro formation of benzo(a)pyrene-7,8-dihydrodiol was more than three-fold for both dichloromethane and toluene whereas the formation of benzo(a)pyrene-4,5-dihydrodiol increased more than five-fold following exposure to toluene but less than two-fold after exposure to dichloromethane. Our results suggest that dichloromethane and toluene can modify the metabolism and thereby the toxicity of other environmental contaminants. (Author abstract) (30 Refs)

48. GLUTATHIONE, LIPID PEROXIDATION AND REGULATION OF CYTOCHROME P-450 ACTIVITY.

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Life Sci; 31(8):779-784 1982

Depletion of hepatic glutathione leads to an increase in lipid peroxidation and depression of cytochrome P-450-catalyzed metabolism of the azo dye carcinogen, N,N-dimethyl-4-aminoazobenzene. This contributes to the marked decrease in biliary excretion of N-demethylated metabolites of the dye. Parallel time courses are seen for decreased hepatic glutathione, enhanced lipid peroxidation and depressed excretion of dye metabolites. In vitro metabolism of DAB by hepatic 10,000 g supernatant fractions is depressed by iron only after glutathione depletion. In view of the iron requirement for microsomal lipid peroxidation, it is proposed that glutathione depletion leads to an increase in the intracellular iron available for activation of lipid peroxidation. In this way, glutathione may contribute to the regulation of cytochrome P-450 activity. (Author abstract) (26 Refs)

VIRAL AND IMMUNOLOGICAL ASPECTS OF HEPATOCARCINOGENESIS

49. EVIDENCE FOR NON-CHROMOSOMAL HEPATITIS B VIRUS SURFACE (HBSAG)- AND CORE ANTIGEN (HBCAG)-SPECIFIC DNA SEQUENCES IN A HEPATOMA CELL LINE.

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J Gen Virol; 61(part1):105-109 1982

As demonstrated previously, a 'beta particle' fraction isolated from the cytoplasm of PLC/PRF/5 cells contains hepatitis B virus (HBV)-specific DNA. Here, further evidence is provided that the specificity of the DNA for HBV is represented at least by sequences coding for the surface and core antigen (HBsAg and HBcAg). This was shown by two different hybridization techniques. One of them, the technique of Southern, distinguished these hybrid molecules formed from those containing HBV DNA integrated into chromosomes. The HBV-specific beta particle DNA forms two distinct bands separate from the high mol wt cellular DNA. (Author abstract) (13 Refs)

50. CHARACTERIZATION OF SV40-TRANSFORMED HUMAN LIVER CELLS BEFORE AND AFTER PASSAGE THROUGH CRISIS.

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Intervirology; 17(4):222-227 1982

SV40-transformed human liver cells could be passed through crisis after transfection with various DNAs (SV40, BKV, or salmon sperm). The pre- and post-crisis cells were compared with respect to growth behavior and the state of the viral genome. Comparison of the viral inserts in the pre- and post-crisis cells showed minor changes in the integration pattern of the SV40 DNA after recovery from crisis. (Author abstract) (18 Refs)

51. THE USE OF MONOCLONAL ANTIBODIES TO INVESTIGATE THE CELLULAR EVENTS ASSOCIATED WITH HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Holmes CH, Gunn B, Austin EB, Embleton MJ
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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Monoclonal antibodies to rat hepatocytes were prepared by conventional techniques involving fusion of hepatocyte-immune spleen cells from Balb/c mice with the mouse myeloma, P3-NS1. One of these antibodies, RL23/36, showed preferential reactivity with adult rat hepatocytes, while a second antibody, RL24/72, was much less specific and showed cross-reactivity with a number of other cell types. Both monoclonal antibodies were specific for hepatocytes within the liver and showed no reactivity with hepatic sinusoidal cells. In addition, a third monoclonal antibody, RL24/106, which was produced in the same way, showed reactivity with connective tissue components in both liver and other tissues. The expression of both hepatocyte-expressed antigens is profoundly affected during hepatocarcinogenesis, the RL23/36-defined antigen especially being reduced in a number of dimethylamino-azobenzene (DAB)-induced hepatomas. The cellular composition of a range of lesions induced in the liver by feeding dietary DAB was examined immunohistochemically using these three monoclonal antibodies in conjunction with several commercially-available monoclonal antibodies directed against rat lymphocytes. Cells within these lesions exhibited considerable heterogeneity with respect to both expression of antigens identified by RL23/36 and RL24/72 and also the degree and type of infiltrating cells observed. (no Refs)

52. MONOCLONAL ANTIBODIES TO AFLATOXIN-DNA ADDUCTS (MEETING ABSTRACT).

Hertzog PJ, Lindsay-Smith J, Garner RC
Cancer Research Unit, University of York, Heslington, York, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Aflatoxin B1 is a probable human liver carcinogen found in high levels in certain countries. The potential of antibodies to aflatoxin B1-DNA (AFB1-DNA) adducts is important since they would reflect not only exposure, but actual levels of damage, and permit, to some extent, the much needed study of carcinogenesis in humans. We have raised such antibodies using the guanine ring-opened form of aflatoxin B1-reacted DNA (ro AFB1-DNA) coupled to methylated keyhole limpet hemocyanin as immunogen. Spleen cells from immunized mice were fused with myeloma cells by conventional methods and hybridomas selected in HAT (hypoxanthine, amethopterin, thymidine) medium. Specific and antibody-secreting hybridomas were detected by enzyme-linked immunosorbent assay (ELISA) using microtiter plates with wells coated with ro AFB1-DNA. Positive hybridomas were cloned twice by limiting dilution, then grown in ascites, for the production of high-titer (1:100,000) ascites fluid for use in immunoassays. In standard competition assays, dilute ascites fluid was preincubated with or without an inhibitor, followed by incubation on the plate. The monoclonal antibodies produced reacted specifically with AFB1-reacted-DNA, rather than DNA, and could detect adducts at the levels found in liver DNA from animals dosed with aflatoxin B1. (no Refs)

53. THE EXPRESSION OF ALPHA-FETOPROTEIN AND ALBUMIN GENES IN RAT LIVER DURING CHEMICAL CARCINOGENESIS.

Schwartz CE, Gabryelak T, Smith CJ, Taylor JM, Chiu JF

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Biochem Biophys Res Commun; 107(1):239-245 1982

The expression of alpha-fetoprotein (AFP) and albumin genes in neoplastic and preneoplastic livers of Fischer rats treated with the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene (MDAB) was investigated. The concentration of AFP started to increase in the serum of rats shortly after the initiation of feeding with MDAB (0.06% of the diet). It reached a peak at about 40 days and then decreased dramatically. After 164 days of treatment, serum levels of AFP increased markedly concomitant with the appearance of palpable liver tumors. The final permanent elevation of AFP was associated with the appearance of malignant cells. There was little if any change in the serum albumin concentrations in rats treated with MDAB. Synthesis of AFP in livers of MDAB-treated rats was found to increase in parallel with AFP serum concentrations. Biosynthesis of albumin showed no changes during hepatocarcinogenesis. These results indicate alteration in the control of gene expression during neoplastic transformation. (29 Refs)

54. SINGLE DOSE OF AFLATOXIN B1 RESULTS IN GGT-POSITIVE HEPATIC LESIONS IN SIX WEEKS (MEETING ABSTRACT).

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Fed Proc; 41(3):355 1982

Aflatoxin B1 (AFB1), a potent hepatocarcinogen, is considered so toxic that a single dose large enough to initiate carcinogenesis would kill the animal. A study was undertaken to examine the effect of a single dose of AFB1 on the emergence of gamma-glutamyl transpeptidase (GGT) hepatic foci, an excellent early indicator of hepatocarcinogenesis. Male F-344 rats 28 days of age were fed an AIN-76 diet modified with 1/3 dextrose, 1/3 starch and 1/3 sucrose. Animals were injected ip with 0, 0.05, 0.1, 0.5, 1, 5 and 10 mg/kg AFB1 in dimethylformamide (DMF) at 2.5 mg/kg. All rats given 5 and 10 mg/kg died within 24 hrs. Approx 1/3 of each remaining group died of apparent DMF toxicity within 48 hrs. After 2 wks at least 10 survivors per group were fed a diet containing 0.05% phenobarbital (PB) to promote the AFB1-initiated lesion. Five animals per group were sacrificed at 6 wks post injection, and livers were examined for GGT-positive foci. Animals receiving 1 mg/kg AFB1 had more lesions than the 0.5 mg/kg AFB1 whereas the 0.1 mg/kg AFB1 animals showed only bile ductular involvement. No foci were observed in the 0.05 mg/kg AFB1 or control rats. In summary, a single dose of AFB1 coupled with the DMF and PB effects resulted in GGT-positive foci as early as six wks after AFB1 injection. (no Refs)

CYTOLOGICAL AND HISTOLOGICAL CHANGES IN HEPATOCARCINOGENESIS

55. THE BIOLOGY OF CHEMICALLY-INDUCED RODENT LIVER TUMORS (MEETING ABSTRACT).

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No affiliation given

International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

It is a common experience in experimental studies as well as in humans to observe liver cells or hepatocyte nodules in livers prior to and in association with hepatocellular carcinoma. The significance of these nodules in the development of liver cancer has been a subject of interest for decades. However, the majority of human and experimental studies have failed to clarify this, mainly because of the complexities of the models used. Our recent studies, as well as studies of others, have shown clearly that metastasizing carcinoma can occur in nodules induced with five different carcinogens, thus implicating nodules as one site of origin for liver cancer. Under many circumstances, the number of nodules induced by an initiating carcinogen is far larger, often by a factor of 100 or more, than is the number of cancers. The vast majority of nodules, which we prefer to designate as hyperplastic, undergo a complex process of remodeling to normal-looking liver and thus regress. A minority may persist and a further subset of these may act as sites of origin for unequivocal liver cancer. It is not known but it is doubtful that the cells in remodeled nodules return to completely normal liver. The remodeling is accompanied by loss of markers gained and gain of markers lost. Clearly the genesis of nodules and the options available to them will have to be clarified in detail before the role of any single nodule in liver cancer development can be delineated. (no Refs)

56. PHENOTYPIC PROPERTIES OF PRE-NEOPLASTIC LIVER LESIONS (MEETING ABSTRACT).

Williams GM

No affiliation given

International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The phenotypic properties of liver lesions believed to be involved in neoplastic development are important indicators of the nature of the abnormalities in the cells of the lesions as well as useful markers for the identification of the lesions. Properties that have been extensively studied include alpha-fetoprotein production, enzyme abnormalities, resistance to iron accumulation and resistance to the cytotoxic effects of xenobiotics. One of the most significant hepatocellular lesions that arises during liver carcinogenesis is the altered focus. This lesion appears early in hepatocarcinogenesis and may give rise to both neoplastic nodules and carcinomas. Foci can display reduced glucose-6-phosphatase activity, reduced adenosine triphosphatase activity and increased gamma-glutamyl transpeptidase activity, but there is often considerable heterogeneity in the pheno-types of foci. Foci appear to be uniformly resistant to iron accumulation and to the cytotoxic effects of xenobiotics requiring biotransformation. Ultrastructural studies have re vealed prominent alterations of the endoplasmic reticulum and plasma membrane. Collectively, these abnormalities indicate that foci are truly a new altered population. Using histochemi cal markers, the induction of foci can be measured as a quant tative index of hepatocarcinogenicity by genotoxic carcinogens. In addition, determination of the effect of xenobiotics on foci induced by genotoxic carcinogens can be used to assess the capacity of chemicals to modify the process of liver tumor development. (no Refs)

57. STUDIES ON INITIATION OF HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA IN THE RAT.

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Diss Abstr Int [B]; 42(10):4024-B 1982

Experiments were designed to: (i) determine whether the enhancement of hepatocarcinogenesis by cell proliferation could be mediated, at least in part, by an increase in initiation, and if that were the case, whether one round of cell proliferation must occur prior to the repair of a carcinogen-induced critical lesion. Initiation was assayed by selectively stimulating the initiated cells to grow into foci of gamma-glutamyl-transpeptidase (GGT)-positive hepatocytes. (ii) determine whether the replication of carcinogen-damaged DNA is important for the participation of cell proliferation in initiation. Hydrocortisone (HC) was given to N-methyl-N-nitrosourea (MMU)-treated animals in mulitple doses in order to inhibit DNA synthesis following PH (partial hepatectomy) (iii) identify the lesions induced in DNA by the carcinogen which permits in vivo replication. (iv) determine the fate of initiated cells. The results obtained indicated that foci of GGT-positive hepatocytes were seen only in rats that received MNU coupled with a cell proliferative stimulus such as PH, but not when such a stimulus was absent. The cell proliferative stimulus had to be given within 24 hours following the carcinogen administration to obtain the maximum number of foci. Similarly, hepatocellular carcinoma was observed 1 year after initiation only when the administration of MNU was coupled with PH. (no Refs)

58. SEQUENTIAL OBSERVATION OF PRE-NEOPLASTIC LESIONS IN THE LIVER OF RATS TREATED WITH N-NITROSODIETHYLAMINE FOLLOWED BY 2-ACETYLAMINOFLUORENE OR ALPHA-HEXACHLOROCYCLOHEXANE (MEETING ABSTRACT).

Ito N, Tsuda H, Hasegawa R, Imaida K
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The aims of this study were to observe the sequence in which hepatocellular carcinomas develop from early preneoplastic lesions and to define hyperplastic nodules (HN) as an indicator of preneoplastic lesions. F344 rats were injected intraperitoneally with N-nitrosodiethylamine (DEN) (200 mg/kg BW) and fed basal diet for first 2 weeks, and then basal diet containing 2-acetylaminofluorene (2-AFF) (0.02%) or alpha-hexachlorocyclohexane (alpha-HCH) (0.1%) for 6 weeks and again placed on basal diet until week 50. Two-thirds partial hepatectomy was performed at the end of week 3. Animals were killed in week 4, 6, 8, 10, 20, 30, 40 or 50 of the experiment. In the liver of rats treated with 2-AAF after DEN, the number of area and HN were maximal in week 10, and then gradually decreased to week 50. However, the area remained almost constant from week 30 to 50. In the group given alpha-HCH after DEN, the number of HN decreased temporarily in week 20 and then gradually increased; the area of HN increased slowly throughout the experiment. Histologically, decrease of HN after week 10 was apparently due to their degeneration or dissappearance. Therefore, the fate of the numbers and areas of degenerated or necrotic nodules which had a spongy or cystic appearance were also examined. The number and area of these degenerated hyperplastic nodules (DHN) increased with time until week 30 and then decreased or remained almost constant in rats given 2-AAF or alpha-HCH. Maximal number of hepatocellular carcinoma was shown at week 40. These results indicate that HN increased continuously in number and area during feeding with 2-AAF, a potent hepatocarcinogen, or alpha-HCH, a weak one. They reached a maximum in week 10 and then gradually decreased, with reciprocal increase of DHN and eventual appearance of hepatocellular carcinomas from week 20. (no Refs)

59. A COMPARISON OF CARCINOGEN INDUCED OVAL CELL PROLIFERATION AND CHEMICALLY INDUCED BILE DUCT PROLIFERATION IN RAT LIVER (MEETING ABSTRACT).

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Fed Proc; 41(3):378 1982

' Oval' cells which appear in the livers of rats exposed to chemical hepatocarcinogens are believed to be of bile duct origin. In order to study this, alphafetoprotein (AFP) production and morphologic changes in the livers of rats fed 0.05% N-2-fluorenylacetamide in a choline devoid diet (CD-FAA) were compared to those induced by feeding 0.15% 4,4'diaminodiphenylmethane (DDPM). Following a two-week feeding of CD-FAA, proliferation of 'oval' cells begins in the portal area and extends rapidly across the liver lobule. Bile duct-like structures are found throughout the liver lobule as a late component of oval cell proliferation. Associated with these changes is a rapid and high elevation of serum AFP and many of the oval cells and duct-like structures contain AFP and albumin when examined by immunofluorescence. Normal bile ducts do not contain AFP or albumin. In contrast, DDPM produces a progressive proliferation of bile ducts, extending from the portal area into the adjacent liver lobule. This is not associated with AFP elevation in the serum and the newly formed ducts do not contain AFP or albumin. It is concluded that the duct-like structures seen as a component of oval cell proliferation do not necessarily represent differentiation of oval cells into bile ducts. Oval cells may have a stem-like capacity to form cell types not seen in the normal adult or fetal liver. (no Refs)

60. CHEMICALLY INDUCED HEPATOCELLULAR PROLIFERATIVE CHANGES IN THE RAT WITHOUT EVIDENCE OF NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

Sparano BM, Brecher MP, Gordon G, Iatropoulos MJ, King CD, Noble JF
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The hypothesis that hepatocellular proliferative changes give rise to autonomous, neoplastic lesions was tested by the present study in which hepatoproliferative lesions induced in rats by an experimental psychoactive drug, cyproximide [1-(p-chlorophenyl)-1,2-cyclopropanedicarboximide] were examined at various times during the course of a 24 month study. A total of

610 male and female Sprague-Dawley rats were distributed into three groups: each of two treatment groups contained 230 rats that received either 0.1% or 0.4% of cyproximide in the diet. One hundred and fifty rats received a drug free diet and served as controls. Five males and five females from each group were sacrificed for postmortem examination after 6, 12 or 20 months of drug diet feeding, after which the remaining rats were retained for recovery (nontreatment) periods of 18, 12 and 4 months, respectively. An additional 25 males and 25 females from each dose level were treated for 24 months and then sacrificed along with all surviving recovery and control rats. Postmortem examinations were performed on all animals; liver weights were recorded, and livers from all animals were evaluated histopathologically. Livers from selected animals were examined electron microscopically. Dose and time related liver changes were observed and consisted of enlarged centrolobular hepatocytes containing proliferated smooth endoplasmic reticulum, pigment deposition, hepatocellular vacuoles and cystic spaces, foci and areas of hepatocellular alteration, basophilic foci, hyperplastic foci and nodules, and hepatocellular tumors. The results of this study demonstrated that while the incidence of proliferative lesions was higher in the livers of treated rats (especially females) than in control rats, the incidence of hepatocellular tumors was the same in treated and control groups and nodular lesions were seen only after 18 months of continuous drug diet feeding. (no Refs)

61. PEROXISOME PROLIFERATOR-INDUCED CARCINOGENESIS: SEQUENTIAL HISTOLOGIC STUDY OF THE RAT LIVER (MEETING ABSTRACT).

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Fed Proc; 41(3):378 1982

Studies of sequential histologic changes of rat liver during hepatocarcinogenesis with hypolipidemic peroxisome proliferators are lacking. In the present study, we have examined the sequential steps of liver carcinogenesis in male F-344 rats fed Wy-14,643 ([4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid), a peroxisome proliferator, at a dietary concentration of 0.1% (wt/wt) for 10, 30, 35, 40, 50, 60 and 70 weeks. The livers were analyzed for light and EM (electron microscopy) changes, 3H-thymidine autoradiography and autofluorescence. At 10 weeks hepatocytes were markedly enlarged and several contained multiple prominent nucleoli. By 30 weeks multiple discrete foci of altered hepatocytes (acidophilic foci) were evident. Between 35 and 50 weeks there were grossly visible nodules of 3-5 mm in size containing cells with similar morphological features as in acidophilic foci. After 60 weeks, all animals contained large greyish tumors. All these tumors were well to moderately differentiated hepatocellular carcinomas with trabecular patterns. H3-thymidine nuclear labeling studies showed a high proliferative activity of cells in acidophilic foci and hepatocellular carcinomas. Uninvolved liver parenchymal cells also exhibited a high labeling index. Progressive increase in the amount of lipofuscin in parenchymal cells of liver was noted in all treated animals. (no Refs)

62. ULTRASTRUCTURE OF ALTERED LIVER CELLS INDUCED BY DIETHYLNITROSAMINE (MEETING ABSTRACT).

Zaki FG

No affiliation given

International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

Several weeks before the development of hepatomas, the livers of young adult Sprague-Dawley rats (of both sexes) dosed IP 3 times a week with 2 mg/kg diethylnitrosamine (DENA) revealed foci of altered hepatocytes entirely devoid of glucose-6-phosphatase and adenosine triphosphatase activity. Although these precancerous cells appeared as normal hepatocytes when examined in H and E-stained paraffin sections, yet they were found to exhibit sites of dedifferentiation with ultrastructural features of hepatoma cells. Early morphological changes indicative of neoplastic transformation took place at the surface membranes of such cells. Such alterations first appeared as marked increase in pinocytotic vesicles along the plasma membranes then as loss of sinusoidal microvilli, capillarization of the sinusoids, protrusion of cytoplasmic blebs in the intercellular spaces, microvillization and infolding of the apposing cell membranes, reduction or loss of desmosomes and obliteration of the bile canaliculi. Subsequent changes were seen as dilation and disruption of the rough endoplasmic reticulum (RER), dispersal of ribosomes, depletion of glycogen, enlargement of the Golgi cisterns and increased number of lysosomes. After 20 weeks, rats given 50 mg/Kg DENA once a week, developed pronounced cirrhotic nodules in addition to multiple hepatocellular carcinoma. In contrast to the neoplastic nodules, the cirrhotic ones retained normal activity of glucose-6-phosphatase and adenosine triphosphatase and exhibited ultrastructural features typical of normal hepatocytes. (no Refs)

63. EFFECT OF DIETHYLNITROSAMINE ON THE RAT LIVER - THE ULTRASTRUCTURE OF HEPATOMA CELLS.

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Acta Anat Sin; 13(1):68-73 1982

The ultrastructure of hepatoma cells induced by diethylnitrosamine in male albino rats was examined with the electron microscope. The nucleus was irregular in shape, and the nuclear membrane was uneven. Nucleoli were larger and irregularly shaped, and the arrangement of nucleolonema was clearly different from that in normal cells. Interchromatin granules were increased but the amount of nucleolus-associated chromatin was decreased. In the cytoplasm, mitochondria were irregular in shape and size, and varied significantly in number from one cell to another. Endoplasmic reticulum exhibited lumina of various widths and concentric bodies. Electron density of the cytoplasm was higher than that of normal liver cells, as was the number of nuclear glycosidic particles. The Golgi body seemed to be longer and the number of layers in flat vesicles was increased. The boundaries between most hepatoma cells were straight, similar to those seen between normal cells. However, some boundaries between hepatoma cells were wave-like and intercalated. The small bile duct was enlarged with varying numbers of microvilli. The number of microvilli facing the Disse's spaces was increased. (26 Refs) (In CHI)

64. THE GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) ACTIVITY OF LIVER LESIONS IN RATS EXPOSED TO AROCLOR 1260 (MEETING ABSTRACT).

Cihla HP, Weltman RH, Pitot HC, Norback DH
William S. Middleton Memorial Veteran's Administration Hospital,, University of Wisconsin Madison, WI, 53705
Toxicologist; 2(1):97 1982

The livers of Sprague-Dawley rats chronically fed Aroclor 1260 (100 ppm for 16 months followed by 50 ppm for 8 months) sequentially developed areas of hepatocellular alteration, neoplastic nodules, and hepatocellular carcinomas. Lesions of ductal morphology consisted of simple and cystic cholangiomas, cholangiofibrosis, and the ductal element of mixed hepatocholangiocellular carcinoma (MHC). Pure cholangiocellular carcinoma was not found. Pathologic lesions were histologically and histochemically assessed. While normal hepatocytes were GGT negative, the earliest hepatocellular lesion demonstrated homogeneous GGT activity and the later lesions were progressively more heterogeneous. Normal bile duct epithelial cells and the epithelia of both simple and cystic cholangiomas were uniformly and intensely GGT positive. The epithelium of cholangiofibrosis was GGT negative, although entrapped areas of neoplastic hepatocytes were GGT positive. The ductal element of MHC was GGT positive. Stromal elements associated with cholangiofibrosis and MHC were GGT negative. Lesions of connective tissue origin, such as fatty infiltration and early fibrosis, and a hepatocellular carcinoma with extreme fatty degeneration with infiltration were GGT negative. (no Refs)

65. HEPATOTOXIC AND CANCEROUS ACTIVATION OF GAMMA-GLUTAMYLTRANSFERASE IN RAT LIVER (MEETING ABSTRACT).

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Cell Physiology Laboratory, Veterans Administration Medical Center, Martinsburg, WV, 25401
Med Pediatr Oncol; 10(1):103 1982

Hepatotoxic compounds benzyl chloride, gamma-hexachlorocyclohexane, carbon tetrachloride, and the pesticide Kerb, and carcinogenic 3'-Me-DAB, administered to Sprague-Dawley male rats in one or two large doses, produced in 24 hrs a striking increase in the liver of the activity of gamma-glutamyl transferase (GGT) and a definite increase of total DNA. An increase in the number of GGT (+) hepatocytes was detected histochemically. In contrast to the induction by 3'-Me-DAB of simultaneous increases of GGT and of the glutathione (GSH) concentration during the period of 24-48 hrs, the increase of GGT produced by hepatotoxic compounds was accompanied by a decrease of GSH which forced GGT to return in 48 hrs to initial values. In hypophysectomized rats hepatotoxic compounds and 3'Me-DAB produced an increase of GGT which rapidly fell to the initial level without any substantial change in the concentration of GSH. From these experiments we concluded that: 1) Increase of GGT alone is not a specific effect of hepatocarcinogens in rat liver, but can be produced by various compounds which are toxic to liver tissue; 2) Not GGT alone, but only the combination of GGT with GSH is the Marker of rat liver carcinogenesis; 3) 3'-Me-DAB inactivates the feedback which keeps the levels of GSH and of GGT constant at the normal values; 4) Hepatotoxic compounds, as long as they do not damage the GSH-GGT feedback, are not carcinogenic for rat liver; 5) In hypophysectomized rats 3'-Me-DAB does not produce tumors because in their livers it is only hepatotoxic and does not become carcinogenic. A model will be proposed of GSH-GGT feedback, its nature, and function. Hepatotoxic effect of a compound has a relatively low affinity for vital receptors and can easily be removed, so that they are not permanently changed. The cancerous effect concerns receptors not essential to the life of the cell and involved in the social rather than the vital functions. The affinity for their receptors is high. (no Refs)

66. OCCURRENCE OF PROGRESSIVE DNA DAMAGE COINCIDENT WITH THE APPEARANCE OF FOCI OF ALTERED HEPATOCYTES.

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Carcinogenesis; 3(6):599-602 1982

The technique of alkaline elution was used to evaluate alterations in nuclear DNA obtained from livers of rats that had received a single 6.6 mg/kg dose of diethylnitrosamine (DEN) during liver regeneration and subsequent exposure (7 days after partial hepatectomy) to phenobarbital (PB). DNA from normal and regenerating liver demonstrated a significant increase in the rate of elution following DEN administration. In those DEN-treated groups that did not receive PB, the rate of DNA elution decreased slowly but failed to return to normal by 44 wk. Exposure to PB hastened recovery of a normal DNA elution profile in normal liver following DEN treatment, and by 44 wk, DNA from these rats eluted at a normal rate. However, in rats treated with DEN during liver regeneration, the rate of DNA elution began to increase at 28 wk of PB exposure and became progressively more rapid through the 36th and 44th wk. This latter group also demonstrated foci of gamma-glutamyl-transferase (GGT)-positive hepatocytes at 28 wk of PB exposure that increased in number and size concomitantly with the increasing rate of DNA elution. At 44 wk, one or more primary hepatocellular carcinomas were present in 73% of the rats in this group; none was seen in any other group. Foci of GGT positive hepatocytes, an increasing rate of DNA elution and eventual primary hepatocellular carcinoma were seen in a group of rats that was begun on PB as late as 85 days after partial hepatectomy and DEN treatment. (Author abstract) (26 Refs)

67. ISOLATION AND TRANSPLANTATION OF PRECURSORS IN HEPATOCARCINOGENESIS (MEETING ABSTRACT).

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Department of Pathology, Schools of Medicine and Dentistry, University of Alabama in Birminghan, Birmingham, AL
Lab Invest; 46(1):57A 1982

The role of cells frequently termed putative preneoplastic cells in hepatocarcinogenesis is still unclear. Two types of cells widely regarded as possible precursors of hepatomas are the 'enzyme-altered hepatocyte' and the 'oval cell'. Both of these cells have histochemically demonstrable gamma-glutamyl transpeptidase (GGT). We have attempted to isolate each of these cell types free of the other to test their biologic potentials. Half a billion liver cells were purified by velocity sedimentation in the Dupont-Sorvall TZ-28 reorienting zonal rotor. When purified preparations of 98.8 per cent hepatocytes were injected into the mesenteric veins of syngeneic rats fed a diet with 0.02 per cent acetylaminofluorene and subjected to partial hepatectomy, all rats developed foci of cells with GGT in their livers in 10 days. Type II cells, small cells with intense GGT, were purified in an isokinetic gradient followed by free-flow electrophoresis. Preparations with 37.2 per cent type II cells and only

1.6 per cent hepatocytes were injected into syngeneic hosts prepared as described above. Recipients of type II cells also developed hepatic foci with GGT within 10 days. Both enzyme-altered hepatocytes and type II cells make up part of what previously has been referred to as 'liver colony-forming units'. (no Refs)

BIOCHEMICAL CHANGES IN HEPATOCARCINOGENESIS

68. METHYLGUANINES IN LIVER DNA AFTER ADMINISTRATION OF HYDRAZINE TO HAMSTERS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:243 1982

Administration of a hepatotoxic dose of hydrazine (Hz) results in the concomitant formation of 7-methylguanine (7MG) and O6-methylguanine (O6MG) in liver deoxyribonucleic acid (DNA) of rats; evidence has been presented to indicate that the source of the methyl moiety in these bases is S-adenosylmethionine. Young adult, male Syrian golden hamsters were given 90 mg Hz/kg body wt po and killed 0, 0.25, 0.5, 1, 6, 12, 24, 48 and 72 hr later. Liver DNA was fractionated by liquid chromatography, with 7MG and O6MG monitored by their fluorescence at an excitation wavelength of 286 nm. DNA methylation was quantitatively detected 15 min after Hz administration, reached half-maximum levels in approx 1 hr, and maximum levels in approx 6 hr which is in close agreement with results from similar studies in the rat. The rate of removal of 7MG is similar to that seen with dimethylnitrosamine (DMN) in the hamster and Hz in the rat. O6MG persisted longer at max levels in hamster DNA than in rat DNA. The higher levels of O6MG in hamster DNA 24 to 72 hr after Hz administration were not the result of continued DNA methylation since incorporation of radiolabel from [3H-methyl]methionine (3H-MET) given hourly 18 to 24 hr after Hz treatment was greatly diminished compared to incorporation from 3H-MET given 0 to 6 hr after Hz. This study demonstrates the similarity in rates of formation and removal of 7MG and O6MG in liver DNA from Hz-treated rats and hamsters to those in DNA from animals treated with carcinogens which are metabolized to direct alkylating agents, such as DMN. (no Refs)

69. CARCINOGEN BINDING AND DNA REPAIR IN PRIMARY CULTURES OF RAT HEPATOCYTES.

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Diss Abstr Int [B]; 42(9):3649-B 1982

The objectives of these studies were to develop an assay with cultured hepatocytes serving as both the metabolizing component and the target cell for cytotoxicity and genotoxicity and to use this system to study three known or suspected carcinogens-senecionine, aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1). Senecionine, a pyrrolizidine alkaloid from Senecio vulgaris, was a potent cytotoxin, as evidenced by the leakage of lactate dehydrogenase from the hepatocytes into the surrounding culture medium and the loss of cells from the monolayer. Senecionine was also genotoxic, stimulating DNA repair. A nontoxic dose of (14C) senecionine was rapidly absorbed by the hepatocytes and converted to more polar metabolites recovered in the culture medium. AFB1 produced by Aspergillus flavus, and a hydroxylated metabolite, AFM1 were both toxic to cultured hepatocytes at very low doses. However, AFB1 was cytotoxic at lower doses than AFM1. The stimulation of DNA repair was apparent at even lower doses than cytotoxicity. AFB1 was again more potent than AFM1, stimulating DNA repair at 0.025 ug/culture, compared to the low genotoxic dose AFM1 of 0.05 ug/culture. The metabolism of a low dose of (14C)AFB1 and (3H)AFM1 by cultured hepatocytes differed significantly. After one hour, only 50% of the (14C)AFB1 remained unchanged in the cultured medium, while 18 hours were required for the same amount of (3H)AFM1 metabolism to occur. (14C)AFB1 and (3H)AFM1 were metabolized to polar metabolites recovered in the aqueous phase after chloroform extraction and to reactive forms which became covalently bound to cellular macromolecules. (no Refs)

70. DOSE- AND CELL CYCLE-DEPENDENT O(6)-METHYLGUANINE ELIMINATION FROM DNA IN REGENERATING RAT LIVER AFTER [14C]DIMETHYLNITROSAMINE INJECTION.

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Cancer Res; 42(9):3814-3821 1982

To study relations between increased transformation sensitivity during DNA synthesis and carcinogen-induced molecular DNA alterations in regenerating liver, the kinetics of formation and the persistence of alkylated DNA bases were determined 10 to 240 min after a single [14C]dimethylnitrosamine (DMN) injection (1.43 and 4.0 mg/kg) during G1 (12 hr after partial hepatectomy) and in synchronized S phase (4 hr after continuous infusion of hydroxyurea after partial hepatectomy; about 80% hepatocytes in DNA synthesis). At 120 min after administration of DMN, the molar fraction of 7-methylguanine reached a maximum which was proportional to the injected DMN dose in G1 but lower by about 25% in S-phase cells. During G1, the molar fraction of O(6)-methylguanine revealed the same formation kinetics as 7-methylguanine; but in S-phase cells, it was reduced by 60% after 1.43 mg/kg and by 35% after 4.0 mg/kg. 3-Methyladenine reached its maximum earlier in S phase than in G1, with a faster decline in S than in G1. As soon as 10 min after DMN was given, the O6-methylguanine/7-methylguanine ratio was significantly lower in S-phase cells than in G1 cells, with a rapid further decrease during 30 min shortly after carcinogen exposure during DNA synthesis. This rapid repair was less expressed after 4.0 mg/kg, indicating an exhaustion of this process after higher carcinogen doses. Cell cycle-dependent differences of the kinetics of O6-methylguanine and 3-methyladenine in DNA in vivo confirm earlier observations in vitro that these adducts are released by different enzymatic mechanisms the activity of which appears to be enhanced during DNA synthesis in rat liver. The faster elimination of the promutagenic O6-methylguanine during DNA synthesis could represent an important but, because of its saturation at higher carcinogen dosages, not sufficiently effective mechanism to protect proliferating cells from initiation during the most critical period of the cell cycle. (Author abstract) (56 Refs)

71. SEQUENCE COMPLEXITY OF NUCLEAR RNA FROM 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOMAS AND HOST CIRRHOTIC LIVER.

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Carcinogenesis; 3(6):609-613 1982

The sequence complexities of nuclear RNAs from 2-acetylaminofluorene-induced rat hepatomas and host cirrhotic livers were compared in RNA-driven hybridization experiments using iodinated single-copy DNA as a probe. Normal liver nuclei RNA hybridized to 10.0 +-0.3% (mean +- SD) of the DNA, indicating an RNA sequence complexity of 3.8 x 10(8) nucleotides. Although nuclear RNAs from cirrhotic livers displayed a greater variation between animals, the mean values for percent DNA hybridized (9.5 +-2.0%) and RNA sequence complexity (3.6 x 10(8) nucleotides) for five cirrhotic livers examined did not differ significantly from normal. Analysis of nuclear RNAs from 10 tumors, 8 of which were classified as moderately to well differentiated histologically, revealed a level of hybridization (9.5 +-1.8%) and a mean value of RNA sequence complexity (3.6 x 10(8) nucleotides) that were almost identical with those for normal liver. Variation in the complexity among tumors was slightly less than that among cirrhotic liver RNAs. These results suggest that while growth characteristics, biochemical properties, and physiology are known to vary between hepatomas and normal or cirrhotic liver tissue, there is no substantial or consistent difference in the RNA sequence complexity of chemically-induced hepatoma cells compared with normal or chemically-induced cirrhotic liver. (Author abstract) (30 Refs)

72. NUCLEOSIDES AND CANCER (MEETING ABSTRACT).

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Fed Proc; 41(3):927 1982

Increased urinary excretion of modified nucleosides and bases, primarily derived from tRNA, is a common feature of mammals with neoplasms. The present study compares the patterns of modified urinary nucleosides and bases of rats with aflatoxin B1 induced hepatomas and dimethylnitrosoamine induced nephroblastomas. Both carcinogens caused marked increases in the same modified nucleosides and bases. However, the quantitative profiles of these excretory products were significantly different. Increased growth of the neoplasms was accompanied by further elevation in levels of these metabolites. Although increased turnover of tRNA, and not cell death, is believed to be the primary reason for the elevated levels in the urine, the data suggest that increased turnover of mRNA and perhaps rRNA are also contributing factors. Specific activities of tRNA from tumor tissue of rats dosed with 14CH3 methionine showed increased incorporation of methyl groups at 4 and 24 hours. The results suggest that the levels and quantitative profiles of urinary modified nucleosides may be useful in the diagnosis of cancer. (no Refs)

73. PURIFICATION AND PROPERTIES OF INORGANIC PYROPHOSPHATASE OF RAT LIVER AND HEPATOMA 3924A.

Yoshida C, Shah H, Weinhouse S
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Cancer Res; 42(9):3526-3531 1982

Inorganic pyrophosphatase (EC 3.6.1.1) has been purified to electrophoretic homogeneity from the soluble portion of the cytoplasm of rat Hepatoma 3924A and rat liver. It has a specific activity of 600 to 700 umol inorganic orthophosphate liberated per min per mg protein at 25 C, a value in the same range as the highly purified enzymes from yeast and Escherichia coli. By all criteria applied, the hepatoma inorganic pyrophosphatase is identical with the liver enzyme. It is a dimer with subunits with molecular weights of approximately 30,000 to 33,000 and has a pH optimum of 7.4, a Km for pyrophosphate of 5 uM, and a Ka for Mg2+ of 0.03 with a pyrophosphate concentration of 0.2 mM. It is not inhibited by high Mg2+ concentrations up to 20 mM. Other metal ions such as Zn2+ and Ca2+ do not activate. Mn2+ activates to less than 10% that of Mg2+ at 0.6 mM and has no effect at 1 mM or higher. In the presence of optimal (4 mM) Mg2+ concentration, Ca2+, Mn2+, Hg2+, and F- at 0.2 mM inhibited strongly, but Zn2+ at 1 mM was not inhibitory. The enzyme had no phosphatase activity toward any of the purine or pyrimidine nucleoside mono-, di-, and triphosphates or toward p-nitrophenyl phosphate, beta-glycerophosphate, glucose 6-phosphate, or glucose 1-phosphate. Bromo- or iodoacetate at high concentration had no inhibitory effect, but p-chloromercuribenzoate and p-chloromercuriphenylsulfonate inhibited strongly at low concentration. The purified enzyme was very unstable but was protected markedly at or above the pH optimum of 7.4 by cysteine, dithiothreitol, and glutathione. (Author abstract) (38 Refs)

74. INCREASED URIDINE DIPHOSPHATE-GLUCURONYLTRANSFERASE ACTIVITY IN PRENEOPLASTIC LIVER NODULES AND MORRIS HEPATOMAS.

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Cancer Res; 42(9):3747-3752 1982

In preneoplastic rat liver nodules produced by 2-acetylaminofluorene, certain uridine diphosphate-glucuronyltransferase (UDP-GT) activities, which are ascribed to a distinct enzyme form, were selectively increased (5-fold). This enzyme form, operationally termed UDP-GT1, accepts 1-naphthol,4-methylumbelliferone, and 3-hydroxybenzo(a)pyrene as substrates and is chiefly inducible in liver by 3-methylcholanthrene-type inducers. Glucuronidation of other substrates (morphine, 4-hydroxybiphenyl, chloramphenicol, bilirubin, and estrone) was only slightly enhanced or decreased in nodular tissue. Differentially increased UDP-GT1 activities were also found in Morris hepatomas 9121 and 7777. Rabbit antibodies to rat liver UDP-GT1, purified from 3-methylcholanthrene-treated rats, demonstrated immunological similarity between the enzymes from liver, nodular tissue, and Morris hepatoma 9121. Rocket immunoelectrophoresis ascertained that enhanced enzyme activity in nodular tissue reflected an increased level of enzyme protein. Increased activity of UDP-GT1 together with decreased cytochrome P-450-dependent monooxygenase may contribute to the resistance of preneoplastic hepatocytes to the cytotoxic actions of chemical carcinogens. (Author abstract) (43 Refs)

75. CHANGES IN ALDEHYDE DEHYDROGENASE PHENOTYPE DURING THE PROMOTION PHASE OF RAT HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Wischusen S, Evces S, Lindahl R
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Proc Am Assoc Cancer Res; 23:228 1982

Hepatomas induced in post-weaning male Sprague-Dawley (SD) rats by sequential dietary 2-acetylaminofluorene (AAF)/phenobarbital (PB) exposure possess an aldehyde dehydrogenase (AlDH) phenotype qualitatively and quantitatively different from that of normal liver. To assess the generality of this phenotype, we have evaluated the ability of other carcinogens and tumor-induction protocols to induce this change. One day old female SD rats were injected ip with either diethylnitrosamine (DEN) or AAF (0.15 uM/gm body wt in corn oil). Animals were weaned onto a 30% protein diet containing 0.05% PB. At intervals up to 18 weeks after weaning, rats were killed and the AlDH phenotype of both normal liver and tumors characterized as outlined below. The NADP-dependent, benzaldehyde-oxidizing, tumor-specific AlDHs were not detected in any normal liver by total activity assays, gel electrophoresis or electrofocusing, or by immunochemical methods. However, a significant change in AlDH phenotype, characterized by high activity with propionaldehyde and NAD was observed in normal liver of some animals receiving PB following either DEN (3/12 by 8 wks) or AAF (5/12). No animals receiving only PB (0/9) nor the basal diet show this change. The new activity is distinguishable from the normal liver AlDHs, and from the tumor-specific and TCDD-inducible isozymes in a number of functional and physical properties, but appears to be closely related to previously described PB-inducible AlDH. (no Refs)

76. SERUM PROTEIN SYNTHESIS BY SOMATIC CELL HYBRIDS.

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Somatic Cell Genet; 8(4):433-449 1982

Serum protein synthesis by rodent hepatoma x fibroblast, hepatoma x teratocarcinoma, and hepatoma x hepatoma somatic cell hybrids was analyzed by Lurell (rocket) and crossed immunoelectrophoresis. Of 22 hepatoma x fibroblast hybrids, 19 synthesized transferrin. Albumin was only synthesized at detectable levels by one hybrid. Alpha-fetoprotein synthesis could not be detected for any of the eight hybrid clones between the mouse hepatoma cell line Hepa 1a and the rat and mouse fibroblasts. Fibrinogen synthesis, or that of five other serum proteins synthesized by the rat hepatoma cell line Faza could not be detected for nine hybrid clones between Faza and rat or mouse fibroblasts. Reduced transferrin and albumin synthesis by rat hepatoma (Faza) x mouse hepatoma (Hepa 1) hybrids in comparison with parental cells indicated that causes other than differentiation state of the cells played a role in limiting plasma protein synthesis in somatic cell hybrids. Specific repression of the transferrin gene may be involved. Alphafetoprotein synthesis occurred in the Faza x Hepa 1 hybrids, yet neither parental strain produces this protein. The absence of transferrin and albumin synthesis by hepatoma x teratocarcinoma hybrids may be due to repression by the teratocarcinoma gene. Transferrin is apparently unique among serum proteins in being synthesized by hepatoma x fibroblast cell hybrids. (23 Refs)

77. VITAMIN B6 METABOLISM IN LIVER AND LIVER-DERIVED TUMORS.

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Cancer Res; 42(9):3538-3543 1982

Vitamin B6 metabolism has been investigated in several highly and well-differentiated Morris hepatomas. Comparisons have been made with two poorly differentiated Morris hepatomas, with host livers obtained from tumor-bearing animals, and with fetal, neonatal, and adult rat liver. The pyridoxal phosphate content and the activities of pyridoxine kinase and pyridoxine phosphate oxidase of all Morris hepatomas examined were significantly less than those in adult host or control livers and generally fell in the range determined for fetal and neonatal liver. A similar pattern was not evident for the activity of pyridoxine phosphate phosphatase. Relative to control and host livers, the activity in hepatomas of the pyridoxal phosphate (PLP)-dependent enzyme, ornithine decarboxylase, was generally elevated. Dexamethasone, at a dose which caused an elevation in the activity of PLP-dependent tumor tyrosine aminotransferase, had no effect on PLP metabolism. The data indicate that tumor progression in the Morris hepatoma spectrum in relation to vitamin B6 metabolism falls into an oncodevelopmental pattern characterized by a diminished amount of tissue PLP and a diminished capability to metabolize precursor vitamer forms to PLP. (Author abstract) (37 Refs)

78. NICKEL DISTRIBUTION AND DNA LESIONS INDUCED IN RAT TISSUES BY THE CARCINOGEN NICKEL CARBONATE.

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Cancer Res; 42(9):3544-3549 1982

DNA lesions in nuclei isolated from rat tissues following ip injection of the carcinogen nickel carbonate were measured by the alkaline elution technique. Kidney, liver, lung, and thymus gland nuclei were examined at 3 and 20 hr after treatment for the presence of DNA single-strand breaks and cross-links. Single-strand breaks were detectable in lung and kidney nuclei, and both DNA-protein and DNAS interstrand cross-links were detectable in kidney nuclei. No DNA damage was observed in liver or thymus gland nuclei. A dose response to both single-strand breaks and cross-links was observed in kidney nuclei. Time course studies revealed that maximum DNA damage in kidney nuclei occurred at 2 to 4 hr following injection and also revealed the presence of an active repair process in these nuclei. Repair-resistant DNA-protein cross-links were observed to persist through 48 hr. Tissue and intracellular nickel concentrations as measured by electrothermal atomic absorption spectroscopy were observed to correlate with the levels of DNA damage and repair. A dose response to the concentration of nickel in tissues and nuclei was observed. These results are discussed relative to the solubilization, toxicity, and carcinogenicity of nickel compounds. (Author abstract) (45 Refs)

79. GROWTH OF HUMAN HEPATOMA CELL LINES WITH DIFFERENTIATED FUNCTIONS IN CHEMICALLY DEFINED MEDIUM.

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(c/o Sato) Div. Pathology, Cancer Inst., Okayama Univ. Sch. Medicine, 2-5-1 Shikata-cho, Okayama 700, Japan
Cancer Res; 42(9):3858-3863 1982

A human hepatoma cell line, HuH-7, which was established from a hepatocellular carcinoma, was found to replicate continuously in a chemically defined medium when the medium was supplemented with Na2SeO3. The cells grew better in this medium than in serum-containing medium without any adaptation period. Other established human hepatoma and hepatoblastoma cell lines, HuH-6 cl-5, PLC/PRF/5, huH-1, and huH-4, also grew in the defined medium. Although HLEC-1 cells failed to proliferate continuously with Na2SeO3 alone, they grew if a cell-free conditioned medium from HuH-7 cells was added to the medium. These cell lines, except the HLEC-1 cell line, produced the following human plasma proteins among those examined: albumin, prealbumin, alpha1-antitrypsin, ceruloplasmin, fibrinogen, fibronectin, heptoglobin, hemopexin, beta-lipoprotein, alpha2-macroglobulin, beta2-microglobulin, transferrin, Complement Components 3 and 4, and alpha1-fetoprotein. Beside plasma proteins, the media from HuH-7, HuH-6 cl-5, PLC/PRF/5, and huH-1 contained anti-carcinoembryonic antigen-reactive proteins, and those from PLC/PRF/5, huH-1, and huH-4 medium contained hepatitis B surface antigen. These proteins were detected during periods of serial cultivation over 9 mo under the above culture conditions. The hepatoma cell lines grown in the fully defined synthetic medium may provide a new approach for investigating the growth and metabolism of human hepatoma cells in vitro. (Author abstract) (35 Refs)

REVIEWS AND OTHER RELATED STUDIES

80. GROWTH REGULATION AND TUMOR PROMOTION BY STEROID HORMONES IN THE RAT LIVER.

Desser-Wiest L

Institut fur Krebsforschung der Universitat Wien, Borschkegasse 8a, A-1090 Wien, Austria

Onkologie; 4(3):120-124,127-132,135-136 1981

Corticosterone both inhibits cell proliferation in the liver of adult rats and synchronizes division of liver cells after partial hepatectomy. By adrenalectomy, corticosterone can be eliminated from the circulation at least for certain time. Additionally it can be inactivated in the liver cell by competitive inhibition of its cytoplasmatic receptor. Both these procedures lead to an increased cellular proliferation. The influence of these processes on the development of chemically induced liver tumors has been investigated. Animals died significantly earlier from hepatomas, when they had been treated with both diethylnitrosamine and steroids belonging to the group of gestagens, androgens and estrogens (which stimulate proliferation). Therefore, a tumor-promoting effect of these substances can be assumed. (Author abstract) (146 Refs) (In GER)

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CHEMICAL CARCINOGENESIS

1. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.
Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.
Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.
Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).
Furst A
Institute of Chemical Biology, University of San Francisco, San Francisco, CA, 94117
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

5. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.
Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
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RADIATION CARCINOGENESIS

6. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 1.
Comptroller General of the United States
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8. RISKS OF NUCLEAR ENERGY AND LOW-LEVEL IONIZING RADIATION. REPORT OF AN AMA ADVISORY PANEL TO THE COUNCIL ON SCIENTIFIC AFFAIRS OF THE AMERICAN MEDICAL ASSOCIATION.
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Dept. Nuclear Medicine, St. Elizabeth's Hosp., Boston, MA
Risks of Nuclear Energy and Low-Level Ionizing Radiation. Report of an AMA Advisory Panel to the Council on Scientific Affairs of the American Medical Association. Monroe, WI, American Medical Association, 40 pp., 1981.

9. ESTIMATION OF RISK OF CANCER INDUCTION IN POPULATIONS EXPOSED TO LOW-LEVEL RADIATION.
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10. EVOLUTION OF THE CONCEPTS AND STANDARDS OF RADIATION PROTECTION.
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15. HOW TO PREVENT CANCER OF STOMACH AND COLON: SMALL MICROBES ARE BIG PRODUCERS OF CARCINOGENS.
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How to Prevent Cancer of Stomach and Colon: Small Microbes are Big Producers of Carcinogens. Stockholm, Stortebecker Foundation for Research, 72 pp., 1981.

16. RELEVANCE OF COLONIC MUCOSAL INFLAMMATION TO AETIOLOGY.
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Cancer; 50(4):788-792 1982

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37. METABOLIC AND MODULATING FACTORS IN TOXICITY AND CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).
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National Center for Toxicological Research, Jefferson, AR

1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

38. PROCEEDINGS OF THE INHALATION TOXICOLOGY AND TECHNOLOGY SYMPOSIUM HELD IN KALAMAZOO, MI, 23-24 OCTOBER, 1980.

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Industrial Toxicology Lab., Upjohn Co., Kalamazoo, MI, 49001

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39. CHEMICAL CLASS SEPARATION AND DETAILED IDENTIFICATION OF GENOTOXIC POLYCYCLIC AROMATIC COMPOUNDS IN AIRBORNE PARTICULATES (MEETING ABSTRACT).

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40. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

Nunziata A, Storino AA

Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy

Vet Hum Toxicol; 24(4):243-247 1982

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